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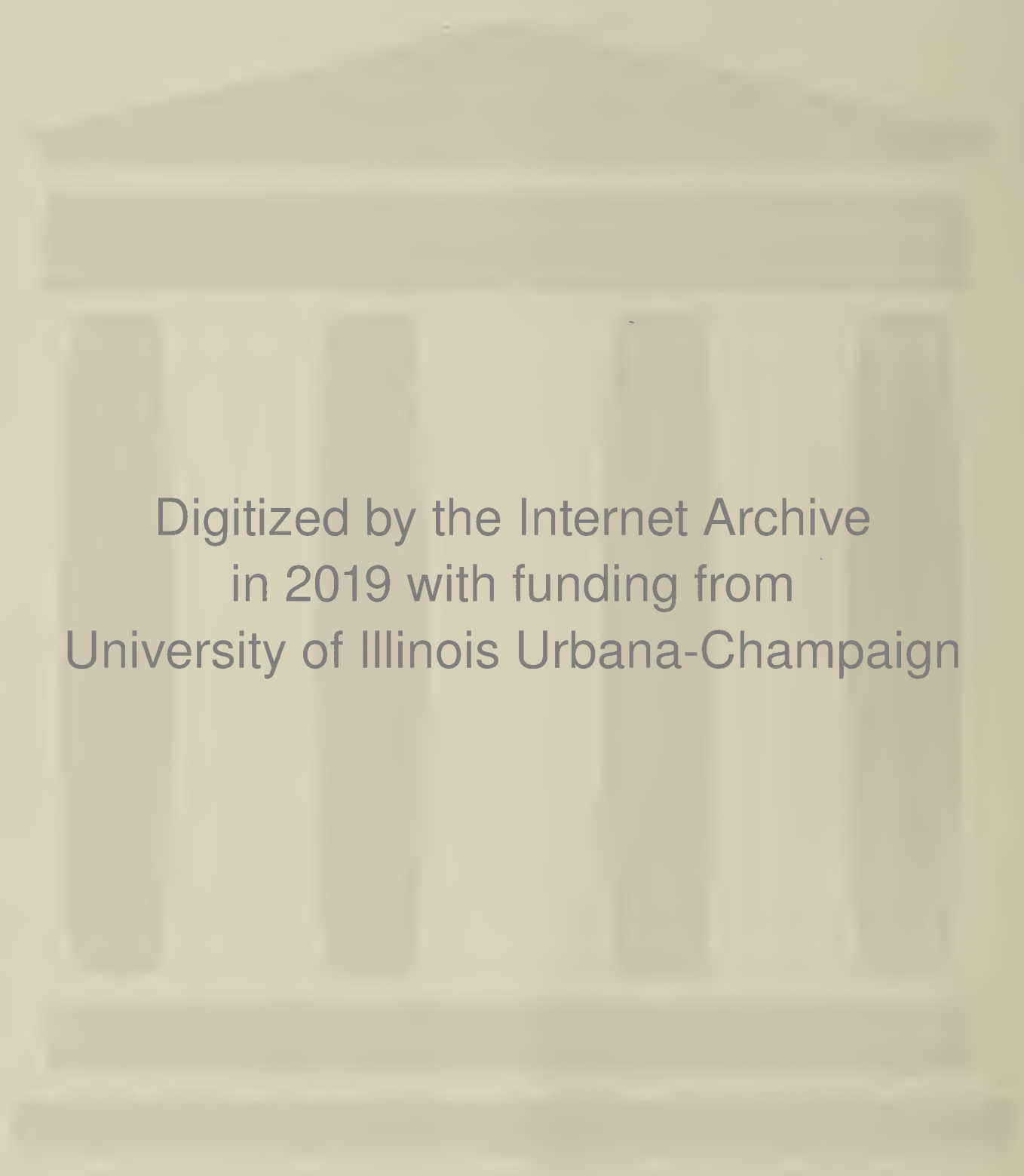
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THE HISTORY OF MEDICINE AS A SUBJECT OF TEACHING AND RESEARCH.*

By DR. ARNOLD C. KLEBS, Lausanne, Switzerland.

In this country no definite place in the scheme of medical education has yet been assigned to the history of our art and science. I shall endeavor to plead its cause in the light of past experience and present achievement. Having taken pains to study the subject during a prolonged residence in Europe, where it has received special attention, I shall try to bring out what seem to me the main features of the work and efforts there. I may state at the outset that, in doing so, I do not wish to recommend blind imitation. On the contrary, I am convinced that in this country an altogether different course might be taken to great advantage and that experience gained abroad can only be used as a pathfinder.

The value of medical history as a desirable feature in medical education has nowhere been more strongly emphasized than here in America by Dr. John Shaw Billings. He was no friend of "the languid scientific swell who thinks it bad style to be practical," but neither did he agree with the physicians who belittle, as interfering with practical efficiency, any effort towards a broader culture, a deeper knowledge and a better understanding of the higher aims of their art and science. Not being nor wishing to be a historian of medicine in the technical sense of the term, although having done fine work in this as in so many other fields, he used the inspiration and the lessons of that history, which he mastered as few have done, for the solution of the problems then before him. The enormous share he has had in the upbuilding of a higher medical education in this country will only be fully appreciated when his quiet activity has become better known. The study

* Read at a meeting of The Johns Hopkins Hospital Historical Club, Dec. 8, 1913.

of the history of medicine and its promotion as a distinct feature of medical education he frequently recommended, discouraging, however, certain methods then advocated and pursued in this direction. In 1883, in addressing the Medical and Chirurgical Faculty of the State of Maryland, he urged the cultivation of local medical history of city and state by that body. Doctors and surgeons, he recommended, would do well to keep historical books on their shelves, and might, without prejudice to their professional capacity, "read something else besides manuals and textbooks." Even at this early date he expressed himself as follows: "It is to be hoped that the scheme of higher medical education which your university is about to organize will include instruction in bibliographical and historical methods as well as in those of the laboratory and clinic."

The late Dr. Eugene F. Cordell, in his presidential address in 1904 at the 105th anniversary of the same faculty, could show how far this hope has materialized, that excellent work is being done at the Historical Club of The Johns Hopkins Hospital, but that only three universities, Pennsylvania, Maryland and Minnesota, have provided a full course of lectures on historical medicine, which seemed to him a very meagre result. This address was commented upon in an editorial in the "London Lancet," strongly endorsing the views expressed in favor of the study of medical history, and adding, as consolation to Dr. Cordell, that his advice needed even more attention in the British Isles, where no university or teaching school of medicine dealt with the subject in any way.

Ten more years have almost elapsed since then, and when we look around now it cannot be said that the study of the

history of medicine has made very decided progress as a feature in medical education. The number of academic courses on this subject is, however, no exact measure of the interest manifested in the subject itself. Their establishment depends largely upon personal and local opportunities, and, where the subject has become a feature, it cannot be said that it enjoys a very great popularity, here or abroad. I believe, however, that this is due more to an inadequate method of procedure than to a lack of interest. That such an interest is continually on the increase hardly needs demonstration. While some years ago a historical consideration of a medical subject was practically never heard of, now we see articles appearing on every side which are evidence that a good deal of historical thinking and studying is in progress. In this relation it might be noted that while we find hidden in special journals and archives abroad masses of valuable and interesting data derived from historical research, similar articles when intended for the profession and appearing in general journals have always to take a back seat and are usually put at the end and in the smallest available type. This is in strong contrast to the procedure here and in England, where one sees not infrequently such historical essays appearing in the most prominent places.

Although by no means all American and English writings can bear comparison with those of an Osler, it is nevertheless interesting, and applicable to a number of English essays, to note what the great German historian Sudhoff has said in the conclusion of a review of Osler's "Alabama Student": "It seems to me that there is a more *echt historischer Geist* in these biographic essays by an English clinician than in many a learned medico-historical work of a German professional historian."¹ It is just this truly historical spirit, recognized by Sudhoff and so brilliantly applied by himself and Neuburger, which is a common characteristic of the historical utterances of many of our physicians. It pervades the speeches and essays of Welch, Weir Mitchell, Abraham Jacobi, and many of their juniors, and it especially formed the quintessence of the gigantic life work of Billings.

I believe there is ground for congratulation and that we have a fertile soil, which, properly tilled and sown, will some day bring forth a bountiful harvest. The student abroad enters the medical school better prepared intellectually than he does here; this is what is being more and more recognized by our educational authorities, and on the success of reform in this direction will depend to a large extent the ultimate, more general establishment of a higher medical education. Only on such a ground can historical medicine thrive and, in return, benefit medical education and medicine in general. The opportunism which has so far characterised the attitude of medical education towards historical medicine will yield to a purposeful determinism as soon as a better preliminary preparation induces the necessary receptiveness in the students.

The question as to whether the moment has come to agitate

the subject cannot be answered in a general way. I believe it has come for certain schools, and others will follow when the fundamental principles are once established and a start is made. In our time the desirability of a broader culture for the physician fortunately needs no special pleading. That this is powerfully promoted by historical knowledge and method is also recognized by many. But as to how this latter is best furthered and utilized to the greatest advantage for the pupil and teacher and for medical art and science in general is a question which I believe has not often received the consideration it deserves.

To start with first principles, it must be admitted that we often overlook the obvious fact that every medical man, consciously or unconsciously, bases his conceptions and their application on those of his predecessors, and that whenever we acknowledge this indebtedness we are to a certain extent using the historical method, for it is fundamentally unimportant whether our predecessors lived five or five hundred years ago. This axiom, in the present case, finds its practical expression mainly in bibliographic search, which every medical man has to take up sooner or later if he wishes to add his share to the sum of knowledge which determines progress. Here again Billings has given pertinent advice when he said (London, 1881) that since there is no lack of men who have the taste and time to search the records of the past, the man who has opportunities of making experiments or observation for himself wastes his time to a certain extent if he tries to do bibliographical work so long as he can get it done for him. "Yet," he adds, "he should know how to make the search, if only to enable him to direct others," advocating also instruction in bibliographic methods. In our days, and especially through the labors of Billings and Fletcher, this task has been greatly facilitated, but none the less few physicians know how to use systematically the aids provided by wise forethought and an incredible industry. Here practical instruction of the student would bear good fruit and demand but little time. He could learn how to select proper references and to give them with accuracy, and, what is still more important, learn to eliminate the useless ones. As Oliver Wendell Holmes said, "there is a dead medical literature, and there is a live one. The dead is not all ancient; the live is not all modern." To distinguish the one from the other is the task of the teacher. It takes long and intimate acquaintance with the matter to develop the necessary judgment, but much useful guidance can undoubtedly be conveyed to a student.

While thus an acquaintance with the literature and an acquisition of bibliographic technique is of primordial importance to any educated physician and can be promoted usefully by appropriate instruction, it forms but a part of that true erudition which is attainable only by a deeper knowledge of the historical evolution of our art and science. A certain kind of erudition, it must be admitted, may superinduce a one-sided philologic and antiquarian standpoint, or, as Billings put it, lead the student off "from his direct research into the many attractive by-paths of quaint and curious speculation."

¹ Mittheil. z. Gesch. d. Med., etc., Leipz., L. Voss, 1909, viii, 448.

This danger must always be kept in mind and be guarded against, but it is no valid argument against erudition as an objective of medical education. "While erudition certainly creates nothing, it leads to creation," said Verneuil.

History primarily demands facts which have to be sought for. Search for them must be undertaken, however, without exclusive reference to the results. There is no reason why medico-historical research should not be regarded in the same light as is any other form of research. When this is once fully recognized the needed workers as well as the means ought to be procurable. Both have been found abroad; they surely can be found here.

The lukewarm interest shown heretofore in historical medicine as a feature in the scheme of medical education ought not to discourage further efforts. If a distinct place were assigned to it in the medical curriculum it could, by its achievements, by the influence it would exert on students and teachers of all departments, form one of the most useful and inspiring features in the whole scheme of medical education. Some such influence is surely needed. We are cultivating too much the purely scientific aspects of medicine; we are depending too exclusively on physics and chemistry to explain life in its various manifestations. Sir Oliver Lodge only lately² has sounded a note of warning which we also may heed. "Biology," he said, "is an independent science, and it is served, not dominated, by chemistry and physics." We physicians, who are applying the lessons of biology, must remember that physical science cannot explain everything; that it furnishes only "proximate explanations." The "philosophic scepticism" voiced by William James, Bergson, and others, gains converts and has led to "a mistrust of purely intellectual processes and a recognition of the limited scope of science." Such a mistrust again finds expression in antagonism to scientific medicine in the serious attention paid by a large public to certain methods of healing not within our scope. Legislation alone cannot counteract these tendencies, and one who has his finger on the pulse of the times will realize that these things cannot be dismissed as passing fads or fashions, or the like, but that there are causes beneath them for which, to a certain extent, we are ourselves responsible. Anything that will, so to speak, humanize our art and science, will not only make us happier, but more satisfied with and proud of our profession and its aims, more inspiring to our students, better friends and helpers to our patients. With history as helpmate we apply "not the experience of one man only or one generation, but the accumulated experience of all mankind in all ages," to use John Herschel's phrase.

REVIEW OF THE LITERATURE.

It is obviously impossible to give anything but a most summary review. To the student who wishes to inform himself in detail about the general historical literature, the following works are indispensable: Choulant (L.), *Biblioth. medic.-hist.*, Lips., 1842, with the additions by Rosenbaum (Halle, 1842); Pauly, (A.), *Bibliographie des sciences médicales*, Paris, 1874; Pagel (J.).

Hist.-med. Bibliographie, 1875-1896, Berlin, 1898; furthermore the library catalogues of the *Bibliothèque Nationale de Paris*, catalogue des sciences médicales, 3 vols., Paris, Didot, 1857-89. All these works except that of Choulant have the common defect of not providing an alphabetical index of authors and subjects, which makes a search most difficult. This difficulty has been most happily obviated in the *Index Catalogue of the Library of the Surgeon General's Office* by the introduction, by John S. Billings, of alphabetically arranged subject key-words as well as the author's names. For the modern literature information is supplied by the *Index Medicus* and the *Mitteilungen zur Geschichte der Medizin*, etc., Leipzig, the latter giving excellent reviews of the literature since 1902. This has also been done by the "Janus," Amsterdam and Leyden, on a smaller scale, since 1896.

The most marked expression of the growing interest in the historical side of medicine is to be seen in the increasing number of articles and books dealing with it. There is an abundance of pleasantly written papers, not particularly profound and often inaccurate. They can only be of real use when the authors are careful enough to state their sources. The excellent custom of prefacing their work with a historical review has been more and more adopted by authors on general and special subjects. In this country biography has probably furnished the theme for the greater part of the literature produced. It is the field most happily cultivated by Osler (*The Alabama Student*, Linacre, etc.), and from it has sprung Kelly's imposing "*Cyclopedia of American Medical Biography*." Billings, Fletcher, Green, Bolton, Weir Mitchell, Garrison, Cushing, Thayer, Roswell Park, Shattuck, Fitz, Locy and others have given us admirable essays on many interesting phases in the evolution of medical thought and practice. Of textbooks worthy of the name only one so far meriting this name has appeared here, the excellent translation by H. E. Handerson (1889) of Baas' "*Grundriss*" (1876). Judging from the advance sheets of the modestly named "*Introduction to the History of Medicine*" kindly put at my disposal by the author, Dr. Fielding H. Garrison, we shall soon be in possession of a home product, which, as regards accuracy, lucidity and mode of presentation, will rival the best of other lands. Here for the first time modern medicine is fully dealt with, occupying more than half the volume. Those stupendous creations of Billings, the *Surgeon-General's Library*, its *Catalogue* and the *Index Medicus*, which the whole medical world envies us, give an unparalleled basis and incentive to solid historical work, not yet sufficiently appreciated here.

In Europe the serious and systematic study of the history of medicine began in the eighteenth century. During the preceding centuries, especially since the invention of printing, what may be called historical work consisted in commentaries on the works of those ancient authors which had appeared in multiple editions. In several of these biographical notes about famous physicians were given, which practice was also followed in certain separate collections of woodcut and engraved portraits.

Among these some deserve an interest even now, notably those of Boissard and Theodore de Bry, Frankfurt, 1597-8; of Sambuco, Antwerp, 1574 and 1603; the *Icones Reusneri*, Strassburg, 1587, and several later ones.

With the end of the seventeenth century, considerable collections of antiquarian interest, books, pictures, gems, coins and other curiosities, had accumulated in the homes of some medical men. Several of these later on laid the foundations of the great museums and libraries of which we are still the beneficiaries. The impetus to sift and study this material and to put it before a greater public issued from two widely separated towns, Geneva and London. Dr. Daniel Le Clerc (1652-1728), son of a physician, a fine Greek scholar, devoted himself very early to the study of the ancients. His "*Histoire de la Médecine*" appeared as early

² President's address, British Assoc., Birmingham, Sept. 11, 1913.

as 1696 and saw many later editions (the best being that of the Hague, 1729), which are profitably consulted to this day. His work, however, covered only the period of ancient medicine up to and including Galen. The learned Dr. John Freind (1675-1728) issued in 1725 his "History of Physick, from the time of Galen to the Beginning of the Sixteenth Century," thereby continuing the work begun by Le Clerc. Freind's book contained important contributions to the subject of Arabic medicine. For the understanding of the periods treated by him later research of the original texts has considerably modified our conceptions. In spite of its deficiencies Freind's book has undoubtedly acted as a stimulus for similar undertakings, especially among English speaking physicians. Several special monographs as well as essays and books on general medical subjects betray this influence. "Mead's *Medicina Sacra*" (1749) and J. Coakley Lettsom's "History of the Origin of Medicine" (1749), followed by the biographical collections of John Aikin (1780) and Hutchinson (1799), are probably the most notable English contributions of that period. Directly inspired by LeClerc and Freind was J. H. Schultze's scholarly "*Historia Medicinæ*" (1728), not nearly as connected and readable a work as its two prototypes, but containing a wealth of antiquarian and especially numismatic information.

The most marked and lasting influence in favor of the historical method in medicine was probably exerted by Boerhaave (1668-1738) and systematically applied by his greatest pupil, Albrecht von Haller (1708-77) in his edition of Boerhaave's "*Methodus Studii Medici*" (1751), in his own "*Bibliothecæ*" (anat. 1774-77, chirurg. 1775, med. pract. 1776) and in the "*Artis Medicæ Principes*" (1769-1772).

Probably no one before and few after him have so successfully utilized in practical work the teachings of history as this founder of modern experimental physiology. To Haller the discoveries and errors of his predecessors and contemporaries served as guidance and control in his own labors, and he did not shrink from the gigantic task of collecting, classifying and annotating all the available literature. Although he has not written a systematic work on the history of medicine, the lesson of his works and teaching, as well as his bibliographic collections, have done signal service in introducing to succeeding generations the advantages of historical thought and method, not the least of his many achievements. For over a hundred years medical historians and bibliographers have benefited by the work of this great man.

Of the historical treatises of the end of the eighteenth century and the beginning of the nineteenth, a few may here be mentioned. Chomel wrote in 1762 an excellent little book on the medical history of France, thereby popularizing local historiography, in which branch some tentative efforts had been made before him. In the seventies Antoine Portal began his great history of anatomy; and Moehsen, the physician of Frederic the Great, published a medical history of Brandenburg and several other important contributions on various historical subjects (medical numismatics and iconography). Here we should also mention the historical dictionary by Eloy (Mons 1778, the first edition of 1755 was wholly inadequate), which brought together a great mass of biographical information. It formed the stock and basis of several later French works.³ Other excellent treatises were furnished in Germany by Gruner (1774), Blumenbach (1786) and Ackermann (1797), but it was the well-known work by Kurt Sprengel (1776-1833)⁴ which inaugurated the epoch of applied re-

search in medical history. The interest of the previous epochs had been centered chiefly in classical Greek, Roman and Renaissance medicine; now, with fresh discoveries of general historians, archæologists and others at hand, new sources for a deeper and wider knowledge were opened and medical students availed themselves of these new opportunities. Sprengel attacked the subject from diverse philosophic points of view or ranged it in distinct epochs and schools, or in relation to the various branches of the healing art. Certain diseases, as, for instance, syphilis, leprosy, the plague and other epidemics, were separately studied.

The principal exponents of this phase of literary work may be indicated in the annexed list,⁵ which, however, makes no claim to completeness and can only serve to mark the cornerstones on which the present generation continues to build.

The abbreviated titles in parenthesis indicate only the general trend of a given work with the date of publication. For living writers only the earliest work appears here. For further details see Index Catalogue, Library S. G. O. and especially the admirable list arranged by Dr. Fielding H. Garrison in 2 series, Vol. XVII, 1912, pp. 89-178, under the title: "Texts Illustrating the History of Medicine."

RESEARCH.

During the period immediately behind us, the first decade of the twentieth century, historical medicine, like history, archæology and medical science in general, has made more rapid progress for various reasons. On the one hand, scientifically trained adepts have increased in number, and on the other, highly improved and specialized methods and instruments of research have been applied. A feature of this advance is that a great number of ancient texts have been brought to light and made available for study by photographic reproduction, transcription and translation. By this means we are increasing and amending continually our knowledge of, for instance, ancient Greek medicine through Arabic and Syriac manuscripts,⁶ into which it has passed in a less altered version than in those from which, after many manipulations during

³Hecker (Medicine, 1822; Epidemics, 1865); Broeckx (Belgian Medicine, 1837; Choulant (Bibliography, 1828-1840; Anatomy, 1852); Henle (Pathology, 1840); von Siebold (Obstetrics, 1839-45); Wüstenfeld (Arabs, 1840); Haeser (Medicine, 1845); Malgaigne (Surgery, 1840); Morejon (Spanish Bibliography, 1842-52); Rosenbaum (Syphilis, 1839; Dermatology, 1844); Puccinotti (Italian Medicine, 1850-66); de Renzi (Salerno, 1859); Flourens (Physiology, 1854); E. H. F. Meyer (Botany, 1854-57); Wunderlich (Medicine, 1859); Virchow (Leprosy, 1860); J. Banga (Dutch Medicine, 1868); Daremberg (Medical Philosophy, 1870); Littré (Biography, 1872); Ingerslev (Scandinavian Biography, 1871-73); Rohlf (German Medicine, 1875-85; Surgery, 1883); Baas (Medicine, 1876); Julius Peterson (Medical Therapeutics, 1877); Hyrtl (Arabic and Hebrew terms, 1879; old German Anatomical Expressions, 1884); A. Hirsch (Geography and Epidemics, 1881-86; Biography, 1884-88); Puschmann (Education, 1884; English Translation, 1891); Predöhl (Tuberculosis, 1888); Charcot & Richer (Art, 1887-89); Proksch (Venereal Bibliography, 1899); Roth (Vesalius, 1892); Creighton (Epidemics, 1894); Sudhoff (Paracelsus, 1894-99); Pagel (Medicine, 1896); Neuburger (Physiology, 1897); Berendes (Pharmacy, 1898); Hirschberg (Ophthalmology, 1899); von Töply (Anatomy, 1898); Fasbender (Obstetrics, 1906); Politzer (Otology, 1907-13).

⁶Galen's anatomy from the Arabic by Max Simon, 1906, and quite recently the book on Syriac medicine by E. A. Wallis Budge, London, 1913.

³The "Biographie Médicale," edited by Panckoucke, 7 vols., 1820-25; the "Dictionnaire Historique," by Dezeimeris et al., 4 vols., 1828-39; and another by Bayle and Thillaye, 2 vols., 1855.

⁴"Versuch einer pragmatischen Geschichte der Arzneykunde," first issued in 1792 and rapidly followed by other editions and additions which were translated into several languages.

the Middle Ages, it came down to us in the first instance. Very much widened have become our conceptions of the ancient medicine of the Mesopotamian, Indian, Chinese and Egyptian civilizations, as a result of the extensive documentary material excavated and made available. America has entered this field of research lately in the edition of the Hearst Papyrus, but there still remain in this country many unexplored treasures which would add to our knowledge of these things.⁷ Much progress has been made in the exploration of mediæval medicine, and evidence is accumulating which shows that the darkness of that age was not so profound as is commonly supposed, and that it can still throw much light.

The medical historian of our day is, however, not satisfied only to decipher the written word of past ages. He attempts, and in many cases very successfully, to obtain direct evidence of the diseases and medical practices of former times. The study of living primitive peoples, which is industriously pursued, gives many hints in this direction. But much interesting information can be obtained from all that excavations have brought to light: bones, mummified bodies, implements, etc. A striking example of this is the story read out of the trephined skulls found in various widely separated districts. American students, Robert Fletcher (1882) to name one, have assisted materially in unravelling the meaning of these finds. Very interesting and valuable are also the results of most original investigations carried on in Egypt and Nubia by English scientists, especially Drs. G. Elliot Smith and M. A. Ruffer. Mummies are being searched for traces of disease (Pott's disease, 1910, facial paralysis, hand deformities, 1912), not only with the naked eye, but also microscopically. The splints found on some bodies have told us most accurately how these people dealt with bone fractures and with what result. With the accumulation of greater material, the mooted question as to the rôle of tuberculosis, syphilis or arthritis in the production of certain alterations found in prehistoric bones as studied by Virchow, Paul Raymond and others, is approaching a solution. None of these findings are so far abundant enough to allow far-reaching conclusions, but they open already a wide outlook and a field of research, which will yield valuable information in time to come.⁸

The realization that artists, humble craftsmen as well as great masters, have from earliest times, depicted with knife, chisel or brush, subjects or scenes of medical interest, has naturally led to a search for such artistic representations. Coins and carved objects had furnished information even to older observers. Paintings of all kinds, including illuminations in manuscripts, have now become the object of minute

scrutiny from the medical point of view. Virchow (1861) may be called the father of this line of research by his analysis of the painting of St. Elizabeth and the lepers by the Elder Holbein. Charcot's more extensive work in this direction was inspired when he saw, in the church of San' Ambrogio at Genoa, Rubens' masterpiece, "Ignatius de Loyola healing the sick."⁹ He was struck by the wonderfully lifelike representation of the possessed woman, which vividly recalled what he had daily observed in his clinic at the Salpêtrière. Paul Richer, then his interne, tells of this and of the beginning of their joint researches on the demoniacs, the sick and deformed in art. These were collected and published in the "Nouvelle iconographie de la Salpêtrière" (since 1888), and brought out by Richer in connected form in that beautiful work "L'art et la médecine" (1900). Similar work has been taken up by many, and from various points of view. Landouzy, Crawford, Peters, Müllerheim, Wickersheimer and others have added most effectively to our knowledge by the study of pictorial representation. The efforts of Holländer, who has given us three monumental contributions on this subject (classical art, caricature, plastic art and medicine), merit separate mention. As a related movement may be considered the establishment of a special department on art at The Johns Hopkins Medical School. Here the main aim is a directly practical one, the teaching of pictorial representation of medical or surgical objects for publication. It seems very likely that, as this work develops, a historical consideration of the subject will become desirable and help to broaden the scope of this interesting departure.

It is regrettable that the results of these researches appear scattered in many different publications, which are in some cases rather difficult of access. The "Mitteilungen" (see footnote 1), the official periodical of the German Society, attempts to review all this work, and succeeds admirably, but naturally the German publications receive the principal attention. With the establishment of more intimate relations between medical historians of the various countries, means will undoubtedly be found by which international co-operation can be assured. A great impetus in this direction was given by the creation of a separate section for the history of medicine at the recent International Medical Congress in London, and its gratifying success brought about through the untiring efforts of its president, Dr. Norman Moore, with the collaboration of such men as Sir William Osler, Crawford, Comrie, Sudhoff, Sticker, Holländer, Meyer-Steineg, R. Blanchard, Wickersheimer, Dorveaux, Barduzzi, Corsini, Capparoni, Walsh and others.

The most important repositories of scientific historical research are the two dignified periodical publications of the Puschmann foundation: the "Archiv für Geschichte der Medizin" and the "Studien" (both Leipzig, J. A. Barth), edited by Karl Sudhoff. They have appeared regularly since 1907 and contain a large number of beautifully illustrated

⁷Very valuable Assyrian documents seem to be available in Philadelphia, and the Central Asiatic treasures of the Field Columbian Museum also await further scrutiny from a medico-historical point of view.

⁸It is significant that a special periodical devoted to the historic biology of pathogenetic agents has begun to appear in Germany: *Zur historischen Biologie der Krankheitserreger*. Edited by K. Sudhoff and G. Sticker (Giessen); 5 parts have appeared since 1909.

⁹Another painting of this same subject, also by Rubens, and of still greater force and interest, can be seen in Vienna.

articles, which are distinguished by accuracy and profound scholarship. These two publications, containing minute analyses of the sources by experts, bring out the new facts or corrections of older conceptions. They are of the greatest value to one who wishes to enter more deeply into the subject. The interested student and practitioner will have occasion to consult them only on rare occasions. In this connection it may be said in general of the literature above enumerated for the purpose of showing the evolution of medical historiography, that it contains very few works which merit study by one in search of historical information for the purpose of writing an article. The teacher ought to familiarize himself with it, but the student need only know where he may find further enlightenment on a given subject not, or only insufficiently, provided in the more recent works at hand. The writing of historical papers from information found in other historical works is devoid of any real value, except in the case of avowed compilations or historical prefaces, and then only when an indication of the sources is given. The field is open to any educated person who has a sufficient interest in the personality, the subject, or the epoch he wishes to discuss. The life and work of some physician, the genesis and evolution of a thought or method, and many other themes, offer plentiful material which can be studied with profit directly from the sources. The early history of American medicine is still a practically unexplored territory and there are surely in many communities valuable data which might shed interesting light on the activities of those men who work under the strain and stress of primitive conditions. Many an object lesson of practical bearing might be so obtained.

There are a few modern treatises or text books which can give to the student a comprehensive view over the immense field of the history of medicine as based on recent research. The voluminous "*Handbuch der Geschichte der Medizin*," founded by Puschmann, was edited by Neuburger and Pagel (3 vols., Fischer, Jena) in 1902 to 1903. It is intended to cover, in a series of articles by different writers, all the periods, including contemporaneous history. Primitive, ancient and mediæval medicine, various special branches and some diseases, are separately treated with an index of subjects for the whole work. This ambitious program has not found an absolutely satisfactory fulfilment. The necessary connection between the different articles is wanting and the articles themselves are of very unequal value. The brilliant introduction which Neuburger wrote for the second volume, and which surveys in masterly style the whole historical evolution, does not compensate for the inherent defects of the whole, although some of the articles have distinct merit. Apparently aware of this shortcoming, Neuburger began to publish in 1906 his "*Geschichte der Medizin*" (F. Enke, Stuttgart). The first volume contains primitive and Oriental medicine and that of classical antiquity. This part has been translated into English by Playfair and prefaced by Sir William Osler (London, 1910). Of the second volume which is to terminate the work, the first part has appeared (1908-1911) and brings the subject down to the

end of the mediæval epoch. Here we have a master-piece of historical synthesis. Nowhere is one bothered by a tedious insistence on irrelevant details, although the author's intimate acquaintance with the results of analytical research is revealed everywhere. Never does he lose the thread which joins the thoughts and accomplishments of succeeding periods, and never does he isolate the history of medicine from that of human culture in general, which would be, to use Billings' phrase (Lowell lecture, 1887), "like cutting a narrow strip from the center of a piece of tapestry and speculating upon the origin and purpose of the cut threads and fragments of pattern that may be found in it." A fascinating, inspiring work which no one interested in the evolution of medical thought and deed can afford to ignore!

It is to be hoped that the second part of this volume will soon appear and that the English translation will speedily follow. Its possession, together with that of Garrison's "Introduction" (1913), will enable the English-speaking student and physician to dispense with any other works. For completeness' sake I must mention a French work, which has appeared lately from the pen of Dr. L. Meunier (Paris, Baillière, 1911). It is a readable treatise which attempts to cover the whole field in condensed form (640 pages sm. 8°). Unfortunately the illness and untimely death of the author have prevented his correcting the many errors in form and substance which have crept into the text, thus making unequivocal recommendation of the book impossible.

EXHIBITIONS AND MUSEUMS.

Special museums for the illustration of historical medicine are of very recent date. The basis was usually formed by a library to which were added curious objects, brought together by one or more collectors. No special plan was followed, only the whims or the good fortune of the individual amateur found expression. The modern museum has a more definite purpose; it attempts to illustrate the evolution of ideas and endeavors in given fields, and maintains the sequence by the substitution of facsimile reproductions where originals are not available. Modern technique has greatly facilitated this aim at completeness. With the realization of the eminent value of objective demonstration in teaching, the technique of museum organization in general has received, of late, very serious attention. The collective objects are not only placed in logically arranged groups, but also in a way to make them readily accessible for demonstration. Museums of historical medicine, if organized and utilized in this way, will surely become a necessary adjunct to every teaching establishment. This feature is as yet in an embryonic state. Still, we can observe some splendid efforts in this direction. Before I enter upon a rapid survey of the achievements in recent years, I wish to call attention to an American undertaking which has a suggestive bearing upon our subject. I mean the educational museum of the Teachers' College, Columbia University, of New York, organized by Prof. D. E. Smith. Here illustrations for lectures on the history of mathematics and of geogra-

phy are collected and supplied to lecturers where needed. The results have been so encouraging that an extension of the museum to other scientific branches is planned.

In this country there does not yet exist a historical medical museum, properly speaking, although there are several promising beginnings. First of all is to be mentioned the Army Medical Museum in Washington, also in part a creation of Billings. It contains much of historic importance, as does also the fine Warren collection at the Harvard Medical School. More specifically historical is the magnificent collection of medical classics in the library of the Surgeon-General's Office.¹⁰ With this collection are exhibited portraits and some objects of medical interest, so that the nucleus of a historical museum may be said to exist. Col. Walter D. McCaw deserves great credit for having thereby materially enlarged and made useful and inspiring this great national library. The incentive to this came to some extent from Baltimore, where the historical spirit has been cultivated for many years by such physicians as Welch, Osler, Cushing, Thayer and others, and has, at times, found expression in demonstrations and exhibits of appropriate objects. Among these, the historical tuberculosis exhibition at Baltimore will remain memorable. As a similar effort may be mentioned the exhibition, arranged by the John Crerar Library in Chicago, in 1907-8, of rare medical works of the Senn collection. The George Washington University of St. Louis, which has recently acquired the library of the medical historian Pagel, will probably soon be prepared for similar work. In the National Museum at Washington there is an interesting collection of objects illustrating folk-medicine, which was prepared by Admiral James M. Flint, Surgeon U. S. Navy (retired).

Holland is the country which has taken the lead in the establishment of medical historical exhibitions and museums. Stokvis, Daniëls, van Leersum and others were, and still are, the principal inspirers. At the fiftieth anniversary of the Netherland Medical Society a historical exhibition was arranged at Arnhem in 1899, the extent and scope of which was much enlarged in a later one held at Leyden in 1907. The Arnhem exposition led to the organization of a permanent one in the States (Stedelijk) Museum in Amsterdam by Dr. C. E. Daniëls, who with great knowledge of the subject and an indefatigable energy, has brought together and most skillfully arranged the objects illustrating Holland's glorious share in the evolution of our art and science.

The great interest manifested in historical medical research in Germany has naturally led to corresponding efforts in this direction. The incentive and continual inspiration has emanated principally from Karl Sudhoff, who in 1898 organized the historical exhibition of medicine and natural science in Düsseldorf, and has ever since been active, directly or indirectly, in many other similar undertakings. With Holländer and Pagel he made his influence apparent in the Berlin exhibition (1906) of "The History of Medicine in Arts and

Crafts," held in the Kaiserin Friedrich-Haus, where a similar permanent museum will probably be established. At the Germanic Museum in Nuremberg, soon after, several rooms were set aside for a medico-historical museum, which is being added to continually. The Historical Museum for Natural Sciences, opened in Munich (1906), has inspired a similar plan for medicine in the same city, but I do not know how far this has materialized. A great feature of the Hygiene Exposition at Dresden (1911) was the historical department, made possible through the efforts and munificence of Dr. K. A. Ligner and organized by Sudhoff and Neustätter. Although limited to the history of hygiene, it formed a most complete objective demonstration of the evolution of medicine from earliest times to our day. Since the closing of the exhibition, the gathering of historical material has been pursued by the directors of this department, and will probably soon assume a permanent form. The very important collection of the Institute for the History of Medicine at the University of Leipzig I shall consider in connection with the subject of teaching.

In England, where collecting has been a sort of national hobby, treasures have accumulated from an early date. Medicine has profited by the labors of Sloane, Mead, Freind and Hunter in this direction. The British Museum, the collections of the Royal College of Physicians, and the Hunterian Museum at the Royal College of Surgeons in London, are storehouses of priceless treasures of interest to us. But the most notable and specifically directed effort has found its happy *dénouement* in the opening on June 24th of this year (1913) of the Historical Medical Museum in London. The bulk of the objects here brought together were collected by Mr. Henry S. Wellcome with great wisdom and a generous disregard of expenditure. His purpose was, as he expressed it himself, "not simply to bring together a lot of curios for amusement," but to make it "useful to students and to all those engaged in research," because he had found "that the study of the roots and foundations of things greatly assists research and facilitates discovery and invention." He intends to make the museum a permanent one. To Mr. C. J. S. Thompson and Dr. Louis W. Sambon has been assigned the formidable task of finding, collecting, classifying and arranging the exhibits. They have discharged it with signal success, and there are few aspects which have not found ample illustration. Many valuable object lessons are contained in these exhibits, a fact to which Sir Frederick Treves, at the opening ceremonies of the museum, alluded in the following words: "One cannot help noticing in this museum, so far as the art and science of surgery is concerned, in what narrow lines progress has been made; and knowing that and studying it, one can forecast to some extent in what direction progress in the future will move."

London offered this summer another historical exhibition of interest to physicians, at the British Museum. Here, in the King's Library, was displayed in chronological order an admirable collection of medical manuscripts, books and illus-

¹⁰ For detailed description see Jour. Am. Med. Assoc., 1911, lvi, 1785-1792.

trations, which no other single institution would be able to duplicate.

In France, historical museums exist only, as far as I know, in Rouen and Lyons. In the latter city one has been organized as an adjunct to the University through the efforts of Prof. Lacassagne. In Paris, such a museum has been planned for some time by the medical faculty, and the dean, Prof. Landouzy, is making every effort to complete the collections, so that in the near future the plan will become a reality. An interesting historical museum on vaccination has been established just outside Tours by Dr. Edmond Chaumier.

THE TEACHING OF HISTORICAL MEDICINE.

Courses of lectures, given by academic lecturers or professors to students, are a novel feature in some of the European universities. The holder of the chair in some cases receives a salary, but usually the positions are honorary ones and the lectures are delivered gratuitously. Nowhere, I believe, are these courses obligatory nor are examinations held on the history of medicine. In Great Britain there are, so far as I know, only two lectureships, one in London, founded on the advice of Dr. Norman Moore by Dr. Fitz-Patrick's widow at the Royal College of Physicians. The lecturers have been J. F. Payne, Norman Moore and Sir Clifford Allbutt; the other at the University of Edinburgh, where J. C. Comrie has lectured. In Germany courses are given at Leipzig (Sudhoff), Jena (Meyer-Steineg), Freiburg, i. B. (Diepgen), Berlin (Pagel's successor not yet appointed), Würzburg (Helfreich). In Austro-Hungary there are also several chairs: in Vienna (Neuburger and Senfelder), Graz (Schrutz), Budapest (von Györy). In Paris a professor for the history of medicine was appointed for some time among the members of the faculty, the present appointee being Prof. Letulle. At Geneva, a successor to the late incumbent, Dr. Naegeli-Akerblom, has not yet been chosen, and at Basel, Prof. Roth and Prof. His (now in Berlin) and others have lectured on the history of medicine. At Copenhagen, Dr. Maar has just been appointed to the chair of Prof. Julius Petersen, and at Rome the lectures are given by Prof. Pensuti.

From this enumeration it becomes apparent that the custom of establishing such lectureships, although frequent, is by no means universal, and that so far the appointments depend mainly upon local opportunities, not upon a general demand. It lies in the nature of the subject, which has no apparent relation to practical aims, that such a demand will probably never become generally manifest and I must confess that the introduction of such lectures into the already overcharged curriculum does not seem to me to offer adequate advantages. On the other hand, there can be no doubt that just as the individual physician will gain by acquiring a knowledge of the historical evolution of his art and science, so will the medical school, and the question as to the best policy to be followed ought to have the serious attention of those in charge.

Personally, I believe that it will be done best by the encouragement of systematic historical research. Some few physi-

cians will be found who have the time and the inclination to devote themselves exclusively to historical work. If they possess or acquire the necessary knowledge in general history, classic, modern languages and bibliography, and are given proper facilities, they will soon increase the number of those who already take a manifest interest in the history of medicine. This is the available ground to be cultivated and if it is worth doing at all it is worth doing well. History is constantly teaching the statesman, the lawyer, the geographer, and the artist; why not also the physician, who practices the most human art, the development of which has been promoted by various influences, often outside the scope of what we term exact science?

Such reflections, I hope, will lead medical schools sooner or later to take up the matter seriously and to introduce into the range of their activities the cultivation of historical research in some form or other. As an example of how this may be done successfully I think I may best describe, in conclusion, the method pursued and the results obtained at the University of Leipzig.

ENDOWMENT OF HISTORICAL RESEARCH.

I have referred already to some publications of the "Puschmann Foundation." Theodor Puschmann was professor of history of medicine at Vienna. He and his wife both had independent fortunes, which they bequeathed in a joint testament "to the University of Leipzig for the promotion of scientific work in the field of the history of medicine." Puschmann died in 1899 and left his own property to his wife, withdrawing, however, his share in the above mentioned bequest. Frau Puschmann apparently expressed a desire to withdraw, but reconsidered the matter in 1900, which vacillation led, after her death in 1901, to a contest of the will. It was decided, however, in favor of the University of Leipzig after prolonged legal procedure. The sum of about 500,000 marks which thus came to the University, was put into the hands of nine trustees, under the presidency of the rector. Four members of this board are professors of the medical faculty, including the dean and the newly elected professor for historical medicine, whose salary was provided for in the articles of the foundation. The chair was offered to Prof. Karl Sudhoff, then at Düsseldorf, who accepted after the fulfilment of his condition that a research institute should be established. Aside from the superlative capacities of this first incumbent, it is undoubtedly due to the establishment of this institute that great results were obtained, and the authorities showed wise forethought in granting the creation of an entirely novel and untried scheme. During the eight years of its existence an enormous amount of constructive work has been done. It was not until 1906 that adequate premises became available for working rooms and collections. The latter had to be brought together piece by piece, no light task in itself, when one considers the degree of completeness that has been reached at present. All this labor of preparation did little to retard the principal work. Already in 1907 the "Studien" and "Sud-

hoff's Archiv" began to appear. They at once became the rallying-point of those devoted to serious scientific research, true to Sudhoff's principle that "one single fact, corrected or newly obtained through the study of the sources, is worth more to true science than a dozen or more of the most brilliant aperçus." Of course, criticism and attack were not wanting, but such epithets as "paper science," "antiquarian amusements," "useless encumbrance," and the like, thrown at the new venture, soon grew scarce, for it became more and more evident that the results of this earnest and sustained effort, generously put at the disposal of a wide circle, tended to form a bond between diverse efforts, and to promote general respect for medical art and science as a whole.

A detailed description of this institute may be welcome to those desirous of establishing something similar. In its present quarters it occupies a wing of the building of the Zoological Institute and Museum. Besides five well lighted, spacious rooms, it has a laboratory for photographic work. All the materials for study, such as books, photographs, engravings, models, etc., are classified and distributed on shelves, in drawers, or in showcases, distinctly labelled. Thus a student can find, easily accessible, all the available material for the study of a given subject, without having to begin with tedious bibliographic studies. In making the collection, Prof. Sudhoff has not endeavored to bring together original manuscripts, incunabula, first editions, and other objects of great material value, which would have required very large funds. For the purposes in view photographic reproductions or models were thought to serve fully as well. Nonetheless, originals are readily obtainable from other libraries and some choice editions belonging to university and city libraries are permanently accessible in the institute. In this way material is accumulated here from all parts of the world and from every phase of civilization.

In order to give an idea of the extent and method of arrangement of this collection I shall give the inscriptions of the various cases in their sequence. The numbers in parentheses indicate approximately the relative space, in shelves or drawers assigned.

In the first (so-called seminary) room is found the reference library (encyclopedias, dictionaries, biographic and bibliographic works, etc.), general and special historical and philosophical works (48). The room contains also files of medico-historical journals, the catalogue, and lockers for workers.

The second room is given over to the collection of works on medicine from the prehistoric to the Renaissance period. The works are usually so placed that the original texts (or their reproduction) and the commentaries thereon stand separately. The divisions are as follows: Prehistoric and Oriental Medicine: Prehistoric and anthropology (3), Popular medicine and folklore (2), Chinese and Japanese (1), Hebrew (2), Babylonian and Assyrian (4), East Indian (2), Egyptian (4), Greek Medicine: General history, geography and philosophy (3), Hippocratic (5), Natural sciences (2), Galen (3), Alexandrian (1), Aristotle (1), Mystic (3), other Greeks (1), Dioscorides (1), Greek texts in folios (1). Roman to Salernitan Medicine: Roman (5), Byzantine (5), Arabic (3), Monastic medicine (2), Salerno (1). Middle Ages: Mediæval northern, Anglo-Saxon (3), German (3), Roman (1), Mystic (1), Scholastic (1), Surgery (2), Folio texts (1). Renaissance: Medical education, universities (5), Leonardo da Vinci, folios and codices (1). This room contains also an additional

collection of works on hospitals, epidemics and files of journals.

The third room includes mostly the collections on special subjects from the sixteenth century to modern times, and the museum exhibits in the following order: Endemics (1), epidemics (5), pathology (2), physiology (2), anatomy (2), Leonardo da Vinci and Vesalius folios (2); hygiene, medical jurisprudence, clinical and pharmacologic material (14); sixteenth, seventeenth and eighteenth century and corresponding text folios (14); nineteenth, twentieth century, local medical history, otology and dentistry, ophthalmology, surgery, Paracelsus and Fabricius Hildanus folios (14); local medical history, psychiatry, pædiatry, gynecology and obstetrics (7).

The museum exhibit embraces a collection of portraits, caricatures, etc., of physicians (alphabetically arranged on 18 sliding shelves). The four showcases contain under glass various originals and models (some on loan) of instruments, ex-votos, orthopædic and surgical appliances, etc. Below these are placed in about 120 drawers various photographic and other reproductions arranged in suitable groups. Given the great diversity of subjects so illustrated, the advantage to the teacher and student of having them appropriately classified is obvious.

A list of the various headings under which this remarkable collection appears, may be welcome. I give it in alphabetical order of the translation: Adam and Eve; alchemy, allegorical, America, prehistoric, anatomy from MSS.; aqueducts and hygiene (Roman); Arabic, care of sick, hospitals, veterinary medicine, pharmacy; Asia Minor; Asklepios and family; astrology; Babylonian gods and demons, cuneiform texts, medical and magical utensils; bandaging (M. A.); baths in open air, sea bathing, public baths, single baths, foot and hand ablutions; Bathsheba and Sussannah; birth of Mary, of St. John, etc.; the blind; blood-letting; burial; care of wounded, clothing, utensils (ancient Greece); care of children, nursery (antiquity and M. A.); China and Japan; Christ's body; cholera; clothing and bedding; circumcision; cosmetics, Cosmos and Damian, life, cures, types, Cyprus and Crete; Dances of Death; death, suicide; death of Mary, the Saints, resurrection; deformities; demon exorcism; dietetics; dissections; dwarfs; Egyptian texts, gods, physicians, magical, gynecological, utensils; Etruscan gods and donaria; eyeglasses; folklore; pregnancy and obstetrics; Greek MSS. and texts, healing divinities, physicians; healing springs and mineral baths; hermaphrodites; holy healers of the sick (M. A.); incunabula; India; instruments; Israel; the lame and cripples; Leda; leechdom and "Lasstafeln"; leprosy, lice, etc. (M. A.); lying-in room; magicians and witches; mediæval charlatans and quacks, clysters, barbers, natural sciences, instruments, ex-votos, universities; modern MSS.; operations (M. A.); Paracelsus, MSS., localities, friends; papyri; patients; phallic worship; Phoenicians; physicians' costumes; plagues; prehistoric; poet physicians; resurrection (M. A.); Roman healing divinities; Saints (M. A.); stigmata of Christ, etc. (M. A.); suffering of mankind (M. A.); superstition (ancient); syphilis, temples and donaria, Greek; thermal; tooth extraction; urinoscopy; Venus antiqua et moderna; Vesalius and pre-Vesalian anatomy; veterinary.

These rooms, which are daily accessible to workers on special subjects and to students, adjoin two other rooms containing the offices of the director and the secretary, as well as the separate collection of the German Society for the History of Medicine and Natural Sciences.

It is, of course, needless to insist that a perfect equipment is no guarantee for good, useful work. For that is needed guidance and inspiration. But such an equipment as this greatly facilitates the task of the teacher and promotes the understanding by the student. Talks to students given here are always demonstrations and render unnecessary the didactic lecture which heretofore prevailed as the only method of

teaching the history of medicine. Billings, in his memorable address at the International Medical Congress of London in 1881, had some such scheme in mind when he said that instructions in the history and literature of medicine might be of great value, "not only as a means of general culture, as teaching students how to think, but, from a purely practical point of view, in teaching them how to use the implements of their profession to the best advantage—for books are properly compared to tools, of which the index is the handle. Such instruction should be given in a library, just as chemistry should be taught in the laboratory. The way to learn history and bibliography is to make them—the best work of the instructor is to show his students how to make them."

RÉSUMÉ.

Historical study and research, if forming an integral part in the scheme of medical education, will exert a most beneficial influence on student, teacher and medicine in general. Didactic lectures alone are insufficient and time-consuming. Whatever direct teaching is given students would be based best on objective demonstration and practical work in bibliographical and historical methods rather than on systematic historical lectures. Such instruction will best be given in separate premises easily accessible to all departments, where the objects for demonstration should be collected and classified and where special research can be carried on.

JOHN HUNTER: HIS LIFE AND LABORS.¹

By C. W. G. ROHRER, M. D., Baltimore, Md.

For several years I have been pleasantly engaged in collecting the works of John Hunter, the founder of scientific surgery. I now have them complete; and for this reason I venture to bring before you a brief review of the life and labors of one with whose career you already are reasonably familiar.

BIRTH AND PARENTAGE.

John Hunter was born at Long Calderwood, Scotland, on the 13th of February, 1728. Long Calderwood is a small estate still belonging to his descendants, improved by a good stone house two stories high, situated about eight miles from Glasgow, in the parish of East Kilbride, county of Lanark. Here, in the second story room above the kitchen, John Hunter was born. There is some doubt concerning the exact date of his birth, but the one given above accords with that of the parish register.²

Strange to relate, Everard Home, in his "Life of Hunter," prefixed to the first edition of the "Treatise on Blood, Inflammation, and Gunshot Wounds," gives the 14th of July as the correct date. This is manifestly wrong. The 14th

of February is the date on which the anniversary of his birth is celebrated by the Royal College of Surgeons of England, and which he himself observed as his birthday; but "probably", as Stephen Paget writes, "he was born during the night of the 13th-14th and in the room over the kitchen."

He was the son of John Hunter and Agnes Hunter, his wife, whose maiden name was Paul. They were married on December 30, 1707. His father, who appears to have been a small farmer living on his own estate, was descended from a very old Scotch family, probably of Norman origin, the Hunters of Hunterston³ in Ayrshire, whose history goes back

this conclusion by the name of the farm adjoining that in question being likewise Long Calderwood, and no place known to me here having the designation of Calderfield.

I am, Sir, Yours, &c.,

MATTHEW DALGLISH, Registrar.

DR. JAMES WATSON,

153, St. Vincent Street, Glasgow.

COPY OF REGISTER ENCLOSED.

"John, a lawful son procreate between John Hunter and ——— Paul, born February 13th and baptized March 30th, 1728."

Extracted by me from the Register-Book of Births and Baptisms for the parish of East Kilbride, in the county of Lanark, this 28th day of March, 1859.

MATTHEW DALGLISH, Registrar.

In confirmation of the correctness of the registrar's notion, W. Hunter Baillie, the grandnephew of John Hunter, wrote as follows to John F. South, vice-president of the Royal College of Surgeons, under date of April 9, 1859:

"In looking at an old map I have of Long Calderwood farm and mansion, which belong to me, I find that a portion of this small property was called Calderfield, and that the larger portion was named Long Calderwood. Upon this latter stands the house which I have always heard was the birthplace of William and John Hunter. It was externally in good repair when I saw it a few years since, and is still serviceable for farming purposes, such as lodging for farm servants, &c. The house used for habitation by the farmer is on another part of the property."

³The old manor-house of Hunterston, with its tower of great antiquity, is still standing; once a strong-hold, now a farm-house.

¹Paper read at the meeting of the Johns Hopkins Hospital Historical Club, January 13, 1913.

²The following letter from the registrar for the parish of East Kilbride to Dr. James Watson, the president of the Faculty of Physicians and Surgeons of Glasgow, together with the accompanying register, are added as authority for any future biographer of John Hunter, and will doubtless be read with interest:—

EAST KILBRIDE, 29 March, 1859.

SIR:—I HAVE searched the records of Births and Baptisms for this parish and have found the name of John Hunter, and send you the Extract. You will observe that the Christian name of his mother is blank, and the place of birth a-wanting, neither being in the Register. On making further search, I found the name of a sister "Isobel," two years older than John the same omission occurs with the name of the mother; but the place of birth given is Calderfield and I am of opinion that the farm now known as Long Calderwood would at one time be divided into two farms named respectively Calderfield and Long Calderwood a circumstance very common in this Parish and I am led to

to the thirteenth century. He was a man of refinement and of some education, with a high moral and religious sense. He was nearly seventy years old at the time of John's birth, who was the youngest of ten children, five dying in infancy. He died in 1738⁴ at the age of seventy-eight. The mother was the daughter of a respectable citizen of Glasgow. According to M. Baillie, she was "a woman of great worth and of considerable talents." John was thus left, at the age of ten, to her sole care and, although a woman of strong mind, she was particularly indulgent to him. She died on November 3d, 1751, aged sixty-six years.

James, the eldest of the brothers who attained to manhood, was born in 1715. He was brought up to the law, but in 1742 he went to London to visit his brother William, who was at that time a teacher of anatomy, and was so captivated by his brother's pursuits that he relinquished the law to become a practitioner of medicine. Intense application to anatomy impaired his health and made it necessary for him to return to Long Calderwood, where he died of a pulmonary hemorrhage in 1743, in the twenty-ninth year of his age. He was a young man of pleasing address, and brilliant promise. William said of him, that if he had lived to practice physic in London, nothing could have prevented his rising to the top of his profession.

William, born on the 23rd of May, 1718, early rose to unrivalled distinction as a teacher of anatomy in London, attained a professional reputation which could not be exceeded, and a celebrity second only to that of his brother John. He was not only famous as a physician and physiologist, but also as the founder, so-called, of scientific midwifery. It was under the fostering care of this elder brother that John was initiated into those pursuits in which he soon became the rival of his instructor. He died in London, on the 30th of March, 1783, universally mourned and lamented.

The younger daughter, Dorothea, married Rev. James Baillie, the minister at Hamilton, near Kilbride, from whom descended the illustrious Dr. Matthew Baillie, and the no less distinguished Joanna Baillie, an authoress of high repute and one of Sir Walter Scott's closest friends.

BOYHOOD AND YOUTH.

Very little is known of the boyhood and youth of John Hunter. His biographers are unanimous in stating that he was wilful and disobedient, and much given to idleness. At the same time he was good at outdoor games, and observant of nature. While he cared little for books his mind was not wholly inactive, as the following statement concerning himself will show: "When I was a boy, I wanted to know all about the

clouds and the grasses, and why the leaves changed color in the autumn; I watched the ants, bees, birds, tadpoles, and eaddis-worms; I pestered people with questions about what nobody knew or cared anything about."

The above, after all, is perhaps the best education he could have had for sharpening his senses to observe, and bringing his reasoning powers to bear upon problems of the highest interest, in the pursuit of which he was later to become an acknowledged leader. As Sir James Paget said of him: "He was impelled to obtain knowledge by intellectual self-exertion, and like an athlete restless in the exercise of his strength, so he could not rest; he could not but search, and watch, and question nature; he must compel her to answer, and he could set no limit to his search. Within the range of the great world of life he must seek by every method of inquiry, every kind and degree of knowledge."

At the age of seventeen, learning that his brother-in-law, a cabinet-maker at Glasgow, married to a sister whom he dearly loved, was laboring under pecuniary embarrassment, he paid him a visit, and for a time assisted him in his business, not as an apprentice but as a volunteer, working probably at small wages or simply for his board and clothing. It was this circumstance which induced some of his envious contemporaries to assert that in early life he had been a wheelwright or a carpenter;⁵ a statement for which there is not the slightest foundation in truth. For three years he generously aided his brother-in-law, but tiring of an occupation which was in no wise congenial to him, he was seized with a desire to visit his brother William, who had been living for some time in London, and had succeeded in building up a large and lucrative practice, and was growing rapidly in reputation. He wrote to him, asking leave to come and be his assistant in his anatomical researches; or, if that proposal should not be accepted, expressing a wish to enlist in the army. In answer he received a very kind invitation from his brother, and immediately set off for London, where he arrived in September, 1748, about a fortnight before the commencement of the autumnal course of lectures. An arrangement was promptly made by which John became an assistant to his brother. Herein was aroused the latent fire of his remarkable genius, which never ceased to burn from that auspicious moment until the day of his widely-lamented death. His reception in London is described by Professor Samuel D. Gross, in the following words:

The meeting between the two brothers was cordial, and arrangements were at once effected by which John became an assistant in William's anatomical rooms, which, although only recently opened, had already acquired marked celebrity on account of their educational advantages. It was there that young Hunter first became aware of his latent powers, and threw off

A report of the house, written in 1867, says that it has not changed since 1728, except that it was then thatched and is now slated, and two rooms downstairs have been thrown into one. From Hunter of Hunterston was descended Francis Hunter, John Hunter's paternal grandfather.

⁴1738 is the date given by Ottley. According to Dr. S. Foart Simmons, the correct date is October 30, 1741. This would make Hunter thirteen years old at the time of his father's death.

⁵Reference is here made to Jesse Foot's statement, on p. 10, of his "Life of Hunter," which reads as follows:

"A wheelwright or a carpenter he certainly was, until the event of William Hunter becoming a public lecturer in anatomy, changed the scheme of his future occupations, and determined him to accept the invitation of his brother: to lay down the chisel, the rule, and the mallet; and take up the knife, the blow-pipe, and the probe."

the incubus which had so long oppressed his soul. A new life broke in upon him; his ambition was aroused; industry, steady and unremitting, took the place of idleness, and the undecided, wavering, erring youth, stimulated by the new atmosphere in which he was now daily immersed, assumed the attitude and the assured character of the philosopher and the student of nature. Who or what brought about these wonderful changes in the life and conduct of this young man, so sudden, so unexpected? It is not difficult to answer the question. It was simply William Hunter, and the influence of his example. John saw the wonderful things which his brother was doing in building up a great anatomical museum, and it is, therefore, not surprising that his tastes should soon have taken a similar direction.⁹

EARLY EDUCATION.

Hunter's preliminary education had been almost wholly neglected, a lack which was never made good, and which, in his maturer years, he never ceased to regret. Before his father's death he had been sent to a Latin school at Kilbride, where he made no progress in his studies, and from which he was removed. Later he went to the grammar-school of Glasgow, but he had little or no taste for books and preferred sports to study.

He tried to remedy his ignorance of the fundamental branches in 1753⁷ by entering St. Mary's Hall, Oxford, as a gentleman commoner. The motives which led him to take this step are not satisfactorily explained by any of his biographers, but it seems probable that he was urged to do so by his brother and friends. His brother was very anxious that he should abandon surgery and study medicine, which was regarded, and, perhaps not without reason in the then existing state of the science, as a higher branch of the healing art. With this end in view it was deemed very desirable that John should have a sound knowledge of Greek and Latin, as no physician was considered properly educated without it.

The effort, however, proved abortive. Hunter was now twenty-five years of age, and he had no disposition to shut himself up in a college, or to give up the idea, formed soon after he settled in London, of becoming a great surgeon. He looked upon such studies as a waste of time; and in referring to the subject some years afterwards, in a conversation with Sir Anthony Carlisle he thus feelingly expressed himself: "They wanted," he said, "to make an old woman of me, or that I should stuff Latin and Greek at the University; but," added he, significantly pressing his thumbnail on the table "these schemes I cracked like so many vermin as they came before me."⁸

One cannot but regret that Hunter did not carry out the wishes of his friends. A little "stuffing" of Latin and Greek would have been of vast benefit to him, in preventing those errors of style and literary composition which so greatly disfigure and obscure his writings.

MEDICAL TRAINING.

Hunter received much of his inspiration and medical training from three celebrated teachers—his brother, William Hunter, William Cheselden, and Percivall Pott. Symonds,⁹ his brother's assistant in the dissecting room, also gave him much instruction.

Having been duly installed as assistant he set resolutely to work. He took, as it were, a new lease on life. Languor and indecision gave way to steady, unremitting toil, sustained by a definite purpose. It is stated of him that "he did not work in Anatomy, as is usually done, for a few hours in the day, but was employed in it from the rising to the setting of the sun."

The first task assigned to him was the dissection of the muscles of an arm, which was so well and so rapidly done that he was next set to preparing an arm in which all the arteries were injected, and these, as well as the muscles, were to be exposed and preserved. This labor was also performed in so satisfactory a manner as to elicit the highest commendation from his brother, who predicted his future greatness as an anatomist, and told him "he should not want for employment." His proficiency as a practical anatomist was so very rapid that, before the end of twelve months, he was intrusted with the preparation of his brother's subjects for his anatomical lectures.

The summer of 1749 was spent by Hunter at Chelsea Hospital, under the instruction of the celebrated Cheselden. Under this worthy master he learned the first rudiments of surgery, an exceptional opportunity which came to him at the request of his brother.

In the succeeding winter he was so far advanced as to become demonstrator of anatomy, assisting and directing the pupils in the dissecting-rooms, while his brother confined his attention almost exclusively to the regular lectures in the class-room.

The assiduous discharge of these most laborious duties gave Hunter full employment during the winter of 1749-50. During the summer he resumed his attendance at the hospital at Chelsea. In 1751 he entered St. Bartholomew's Hospital as surgeon's pupil to Percivall Pott, another great luminary in British surgery. In 1754 he became surgeon's pupil at St. George's Hospital. In the winter of 1755, seven years after his arrival in London and after he had acted as assistant for five years, he was admitted to a partnership in his brother William's private school of anatomy.¹⁰ Besides a certain portion of the course of lectures allotted to him, he gave lectures when his brother was called away to attend his patients.

PROFESSIONAL CAREER.

Hunter's professional career may be said to have begun in May, 1756, when he was appointed house-surgeon to St.

⁹ "John Hunter and his Pupils," p. 13.

⁷ In the buttery book at St. Mary's Hall the date of Hunter's admission is given as June 5, 1755.

⁸ Ottley's "Life of John Hunter" Palmer's Edition, vol. I, page 14, London, 1837.

⁹ Sometimes spelt "Simmons," and also "Symons."

¹⁰ I have purposely refrained from making even brief allusion to Hunter's differences with his brother William, as these unfortunate occurrences will be fully narrated in a subsequent paper on William Hunter.

George's Hospital, which position he retained, however, only for the short space of five months. The reason of his resignation is not recorded, but it was probably because he longed to return to the more congenial work of the dissecting room.¹¹ He worked for ten years on human anatomy, during which period, as Everard Home informs us, "he made himself master of what was already known, as well as made some addition to that knowledge." Some of his discoveries called forth the highest commendations of Baron Haller, then considered the first physiologist in Europe, and still command admiration. At that time he also began his studies in comparative anatomy, a new and untrodden field of scientific inquiry in which he was soon to become a distinguished authority. Unfortunately, owing to his incessant labors, his health was beginning to suffer. In the spring of 1759 he was attacked with inflammation of the lungs, from which he made a tardy recovery, the disease leaving in its wake certain symptoms suggestive of pulmonary tuberculosis.¹² He was strongly advised to go abroad; and in October, 1760, through the agency of his friends, he was made a staff-surgeon in the army. In the following spring he went with the army to Belleisle, off the western coast of France. He served as senior surgeon on the staff, both in Belleisle and in Portugal, till the year 1763, when peace having been proclaimed, he returned to England, completely restored to health, and settled in Golden Square, London, to start practice as a surgeon. He soon found that his half-pay as a military surgeon, and the emoluments derived from private practice, were inadequate for his support. Therefore, in order to increase his income, he taught practical anatomy and operative surgery for several winters. He also took private pupils, each of whom was apprenticed to him for five years, at a fee of five hundred guineas (about \$2,650.00), which included board and lodging. Among his private pupils whom he continued to receive until within a short time of his death were Edward Jenner, John Abernethy, Henry Cline, Philip Syng Physick, Astley Cooper, Everard Home, and others.

At this time Hunter resumed, with unabated zeal, his researches in comparative anatomy and physiology. Finding that his experiments could not be conducted properly in the midst of a large city, in 1764 he purchased two acres of ground about two miles from London, beyond Brompton, and built upon it a small house to suit himself, well known by the name of Earl's Court.

In 1768 a vacancy on the surgical staff occurred at St. George's Hospital, and Hunter became a candidate for the position. Aided by his brother William, he was elected surgeon to the hospital, where he served until his death, twenty-five years later.

Soon after his appointment to St. George's Hospital he

¹¹ In 1757, at the age of 29 years, Hunter was made Prosector and Demonstrator in Dr. William Hunter's Theatre of Anatomy, in Great Windmill Street (Professor Owen).

¹² There was a tuberculous taint in the Hunter family, James, an older brother of John, dying of "a spitting of blood," in the twenty-ninth year of his age, as stated in a preceding paragraph.

was elected a member of the Corporation of Surgeons. Although the corporation embraced some excellent men, Hunter had so little respect for it that he seldom attended its meetings or took any active part in its deliberations.

In the winter of 1773, Hunter determined to become a public lecturer on the theory and principles of surgery, his reasons for which were usually explained as often as he began his course. He stated that he had so frequently been compelled to hear his opinions either incorrectly quoted, or delivered as the discoveries of others, that he found it absolutely necessary himself to explain them systematically. For two winters he read his lectures gratuitously to the pupils of St. George's Hospital, and in 1775 publicly delivered them in his house in Jermyn Street.¹³

CONTRIBUTIONS TO MEDICAL SCIENCE.

Hunter made many notable contributions to medicine and surgery. Several of his early papers were published, in 1762, in Dr. William Hunter's "Medical Commentaries." These are: An account of his injecting the testis, his description of the descent of that body, with observations on the hernia congenita, and his experiments in proof of the veins not being absorbents.

Among his discoveries in human anatomy, and his contributions to that science, are the following:

He traced the ramification of the olfactory nerves upon the mucous membrane of the nose, and discovered the course of some of the branches of the fifth pair of nerves—the trifacial.

He traced, in the gravid uterus, the arteries of the uterus to their termination in the placenta.

He was the first to demonstrate the function of the lymphatic vessels as absorbents in the human economy.

In the course of his inquiries in comparative anatomy, aided by the results gleaned from animal experimentation, among other things he made the following discoveries, all of which have a distinct bearing upon human medicine and surgery:

He ascertained the changes which animal and vegetable substances undergo in the stomach, when acted upon by the gastric juice.

He discovered, by means of feeding young animals with madder, which tinges growing bones red, the mode in which a bone retains its shape during its growth.

He explained the process of exfoliation by which a dead piece of bone is separated from the living.

In 1776 Hunter sent to the Royal Society a memoir on the means to be employed in the resuscitation of persons apparently drowned. In the same year he was appointed Croonian lecturer by the Royal Society. The subject selected was "Muscular Motion." The course extended over a period of six years, being completed in 1782.

¹³ The task of lecturing, even with his copy before him, was so formidable that he was obliged to take thirty drops of laudanum at the beginning of each course. Yet he certainly felt great delight in finding himself understood, always waiting at the close of each lecture to answer any questions; and evincing evident satisfaction when those questions were pertinent, and he perceived his answers were satisfactory and intelligible (Adams).

The prevention of rabies or hydrophobia early engrossed Hunter's attention, and he was one of the first surgeons who taught that deep excision of the wounded structures is the most successful method of operation.

He also made experiments upon the transplantation of teeth in the human subject, and upon skin grafting.¹⁴

The most remarkable operation associated with Hunter's name is the one in which he tied the femoral artery in the "aponeurotic space in the middle third of the thigh," in what has since been termed, and rightly, "Hunter's canal," for the cure of a popliteal aneurism. This one feat of surgical daring, novel alike for its resourcefulness and originality, is in itself sufficient to give him undying fame. It was performed in December, 1785, at St. George's Hospital. The particulars of this case are given in the London Medical Journal, and in the Transactions of a Society for Improving Medical and Chirurgical Knowledge. The patient, a coachman, forty-five years of age, in six weeks walked away from the hospital cured.

In his "Lectures on the Principles of Surgery" (Palmer's edition, vol. I, p. 551.), he comments upon this operation, as follows:

In December, 1785, I performed the operation at St. George's Hospital, in a case of popliteal aneurism, in a manner different from that ordinarily practiced, and with success. ***** I would only observe, that in future I would advise only tying the artery in one part, and not to endeavor to unite the wound by the first intention. In that case four ligatures were applied upon the artery.

The three important principles on which the Hunterian operation is founded are:

1st. That *the impulse of the blood into the aneurism being restrained by a ligature placed on the artery above the tumor, the further progress of the disease will be checked, without the necessity for a ligature being also placed on the artery below the tumor.*

2d. That *the powers of absorption would suffice for the removal of the coagula in the sac, and the necessity for opening it be thus done away with.*

3d. That *the anastomosing vessels of the limb, in their natural state, would be capable of immediately taking on such increased action as would suffice for carrying on the circulation to the parts below the point at which the main artery was tied.*

It is a singular fact that Hunter foreshadowed the principles which now guide the surgeon in the treatment of club-foot and similar deformities. In 1767 he ruptured his tendo Achillis, a circumstance which led him to institute a series of experiments upon the reunion of divided tendons in the dog.

BOOKS AND PUBLICATIONS.

Hunter's merits as an author are truly great. Notwithstanding his want of scholarship, and the labor with which he composed, he was a prolific writer. Like his celebrated

¹⁴ "May we not claim for him," says Sir Wm. Fergusson, with reference to these experiments, "that he anticipated by a hundred years the scientific data on which the present system of human grafting is conducted?" (*Hunt. Orat.*, 1871, p. 17.)

teacher and older brother, William, he early formed the habit of committing his views to writing, even when he did not intend to give them immediate publicity. Owing to an unfortunate circumstance (the burning of the Hunter MSS., by Sir Everard Home, in July, 1823), much that he wrote never met the public gaze. Many of his early contributions, especially those on comparative anatomy and physiology, found their way into the Transactions of the Royal Society and other similar publications, where they elicited much attention.

Hunter's first systematic work was his "Treatise on the Natural History and Diseases of the Human Teeth," the first part of which was issued in 1771, and the second seven years after (1778).¹⁵ The work was well received, and greatly enhanced his reputation as an acute observer and investigator. His attention seems to have been originally directed to the subject by the deplorable state of dentistry, which was almost solely confined to the barber or ignorant mechanic, whose chief occupation consisted in extracting and plugging teeth.

On pp. 121 and 122, of Part I, in his remarks entitled "Of the Diseases of the Teeth," he says:

The Teeth are subject to diseases as well as other parts of the body. Whatever the disorder is that affects them, it is generally

¹⁵ On the occasion of the publication of Part II, a new title-page was added to Part I, and the two (being bound together) were sold as the *second* edition.

The full title of Part I, which consists of 128 quarto pages, is:

The
NATURAL HISTORY
of the
HUMAN TEETH:
Explaining their
Structure, Use, Formation,
Growth, and Diseases.
Illustrated with Copper-plates.
By John Hunter, F. R. S.
Surgeon Extraordinary to the King, and Fellow of the
Royal Society.

London,
Printed for J. Johnson, No. 72, St. Paul's Church-yard.

MDCCLXXVIII.

The full title of Part II, also containing 128 quarto pages, is:

A
PRACTICAL TREATISE
on the
Diseases
of the
TEETH;
Intended as a
Supplement
to the
Natural History of those Parts.
By John Hunter,
Surgeon Extraordinary to the KING, and Fellow of the Royal
Society.
London.

Printed for J. Johnson, No. 72, St. Paul's Church-Yard,
MDCCLXXVIII.

attended with pain; and from this indeed we commonly first know that they are affected.

Pain in the Teeth proceeds, I believe, in a great measure, from the air coming into contact with the nerve in the cavity of the Tooth; for we seldom see people affected with the Tooth-ach, but when the cavity is exposed to the air.

It is not easy to say by what means the cavity comes to be exposed.

The most common disease to which the Teeth are subject, begins with a small, dark coloured speck, generally on the side of the Tooth where it is not exposed to pressure; from what cause this arises is hitherto unknown. The substance of the Tooth thus discoloured, gradually decays, and an opening is made into the cavity.

Part II consists of ten chapters, treating of a variety of topics. For example, Chap. I, Sec. IV, is devoted to a consideration of gum boils; Sec. VII, to abscess of the *Antrum Maxillare*. Sec. I, of Chap. III, is allotted to a discussion of the scurvy in the gums; while in Chap. IX, the transplanting of teeth is discussed *pro* and *con*. In Chap. X, pp. 126 and 127, he relates the following case where a disorder of the urethra was produced by dentition:

A boy, about two years of age, was taken with a pain and difficulty in making water; and voided matter from the *urethra*. I suspected that by some means or other this child might possibly be affected by the venereal poison; and the suspicion naturally fell on the nurse.

These complaints sometimes abated, and would go off altogether; and then return again. It was observed at last, that they returned only upon his cutting a new Tooth: this happened so often, regularly and constantly, that there was no reason to doubt but that it was owing to that cause.

The text of Hunter's book on the Teeth is embellished by sixteen plates. It also has a copious index. The work passed through three editions, the last having been issued in 1803, ten years after Hunter's death.

The "Treatise on the Venereal Disease" appeared in 1786,¹⁶ followed by a second edition in 1788. A third edition

¹⁶ The first edition was a handsome quarto volume of 398 pages, illustrated with seven full-page plates from drawings made by William Bell, and provided with a most comprehensive index. Its simple, but all-expressive title is:

A
TREATISE
on
THE VENEREAL DISEASE.
By John Hunter.
London,
Sold at No. 13, Castle-Street, Leicester-Square.
MDCCLXXXVI.

The dedicatory page of this pioneer and famous publication is interesting. It bears the following inscription:

To
SIR GEORGE BAKER, Bart.
Physician to Her Majesty,
President of the College of Physicians,
and
Fellow of the Royal Society,
THIS WORK
is inscribed
As a Mark of Esteem,

Leicester-Square,
March 30, 1786.

By His Friend, and
Humble Servant,
John Hunter.

was issued by Everard Home, in 1810. Having been long and impatiently expected, it at once attracted general attention. Hunter had spent many years in collecting his material; his object was to produce a great work, founded solely upon his personal observations. He had seen much of these diseases during his connection with the army, and afterwards in civil practice, and he felt that he could let the work rest upon its own intrinsic merits. His account of venereal affections was for upwards of a third of a century the best authority on the subject in any language, and his description of the indurated chancre is so graphic and distinct that it will always be called by his name. It runs in part as follows:

This, like most other inflammations which terminate in ulcers, begins first with an itching in the part; if it is the glans that is inflamed, generally a small pimple appears full of matter, without much hardness, or seeming inflammation, and with very little tumefaction, the glans not being so readily tumefied from inflammation as many parts are, especially the prepuce; nor are the chancres attended with so much pain or inconvenience, as those on the prepuce; but if upon the frænum, and more especially the prepuce, an inflammation more considerable than the former soon follows, or at least the effects of the inflammation are more extensive and visible. Those parts being composed of very loose cellular membrane, afford a ready passage for the extravasated juices; continued sympathy also more readily takes place in them. The itching is gradually changed to pain; the surface of the prepuce is in some cases excoriated, and afterwards ulcerates: in others a small pimple, or abscess appears, as on the glans, which forms an ulcer. A thickening of the part comes on, which at first, and while of the true venereal kind, is very circumscribed, not diffusing itself gradually and imperceptibly into the surrounding parts, but terminating rather abruptly. Its base is hard, and the edges a little prominent. When it begins on the frænum, or near it, that part is very commonly wholly destroyed, or a hole is often ulcerated through it, which proves rather inconvenient in the cure, and in general it had better, in such cases, be divided at first.

In 1788 a second edition of the "Treatise" was issued, also consisting of one quarto volume, price a guinea. On this work Hunter had bestowed an infinity of time and trouble; and before publication he submitted every part of it to a committee of his friends, consisting of Sir Gilbert Blane, Dr. Fordyce, Dr. David Piteairn, and Dr. Marshall. Both the first and second editions were printed and published at Hunter's own residence.¹⁷

¹⁷ A third quarto edition was published the year after Hunter's death, by Everard Home. This was printed by some mistake from the first instead of from the second edition, and is, therefore, chargeable with all those errors which Hunter was at so much pains to correct. A fourth edition, in one octavo volume, with notes by Dr. Joseph Adams, was published in 1810. This is a pretty correct reprint from the second edition, augmented and elaborated by Adams' Commentaries. Meeting with a ready sale, a second edition of it was called for in 1818. In his preface, Dr. Adams pays Hunter a compliment by saying:

"I would advise every medical student to read the whole of the book in the order in which it stands. He will find it the best introduction to pathological reasoning that his closet can afford him. Those chapters, in the Third Part, which relate to Stricture and other diseases in the urinary passages, may perhaps fatigue his attention without adding sufficiently to his knowledge. It cannot be expected that he should retain the whole in his mem-

Of the "Treatise on the Venereal Disease," Jesse Foot has this to say (Life of Hunter, pp. 272 and 273) :

The sale of it was rapid at first from curiosity being artificially raised, as the papers of the day had announced that it was to throw all former productions at an humble distance.

Hunter's "Observations on Certain Parts of the Animal Economy" was first published in 1786. It is dedicated to Sir Joseph Banks, president of the Royal Society.¹⁸ A second edition appeared in 1792; and in 1837, a third, edited by Richard Owen. The first two editions are quarto; and, like the corresponding ones of the "Treatise on the Venereal Disease," were printed and sold at Hunter's own residence. The third edition, the one by Owen, is an octavo volume of 506 pages.

The "Treatise on the Blood, Inflammation, and Gun-shot Wounds," a work of vast labor and the most patient research, and upon which Hunter's fame as a surgeon and a medical philosopher largely rests, was published in 1794, under the supervision of Dr. Matthew Baillie and Everard Home, only about one-third of the proofs having been revised by the author at the time of his death. A life, by Everard Home, was prefixed to the volume, but this, for some reason, was omitted in the succeeding editions of 1812, 1818, and 1828.¹⁹

ory, and the remarks being chiefly practical, must be referred to as often as intricate cases occur. If therefore these chapters are read in their order, the student must not be angry with his Author or himself, if he cannot keep up his attention to every minutia. Whenever he has an intricate case, in his own practice, he will not accuse Mr. Hunter of prolixity."

A fifth edition, quarto, consisting of 429 pages, with notes by Sir Everard Home, Bart., was published in 1809 and 1810, it being the *second* edition by this editor, in which, however, few deviations from the first are observable. A supposititious title-page, purporting to be the *third* edition, seems to have been added in 1810, in order to increase the sale. The copy which I possess, of this edition, came from the library of Joseph Henry Green, who was president of the Royal College of Surgeons of England, in 1859, when Hunter's remains were transferred from the vault of St. Martin's-in-the-Fields to Westminster Abbey. It has for a frontispiece a print of Sharp's engraving of Reynolds' celebrated portrait of Hunter.

¹⁸ TO SIR JOSEPH BANKS, Bart.,

President of the Royal Society, &c. &c. &c.

DEAR SIR,

As the following Observations were made in the course of those pursuits in which you have so warmly interested yourself, and promoted with the most friendly assistance, I should be wanting in gratitude were I not to address them to you, as a public testimony of the friendship and esteem with which I am,

Dear Sir,
Your obliged and
Very humble Servant,
JOHN HUNTER.

Leicester Square,
Nov. 9, 1786.

¹⁹ The original edition of this splendid work was issued in a quarto volume of 575 pages, with eight plates. Prefixed to it is an account of Hunter's life and writings, consisting of 67

Abernethy, in his "Lectures on Local Diseases," pays the following splendid tribute to this work:

I know of no book, to which I can refer a surgical student for a satisfactory account of those febrile and nervous affections

pages. An engraving of his head forms the frontispiece. The full title of the volume is:

A
Treatise
on
The Blood,
INFLAMMATION,
and
Gun-Shot Wounds,
By the Late
John Hunter.

To Which is Prefixed,
A Short Account of the Author's Life,
By His Brother-in-Law,
Everard Home.

London:
Printed by John Richardson,
For George Nicol, Bookseller to His Majesty, Pall-Mall.

1794.

It is dedicated to his Majesty, the King, in the following laudatory terms:

TO THE KING.

MAY IT PLEASE YOUR MAJESTY,

In the year 1761, I had the honour of being appointed by your Majesty a surgeon on the staff in the expedition against Bellisle.

In the year 1790, your Majesty honoured me with one of the most important appointments in the medical department of the army, in fulfilling the duties of which every exertion shall be called forth to render me deserving of the trust reposed in me, and not unworthy of your Majesty's patronage.

The first of these appointments gave me extensive opportunities of attending to gun-shot wounds, of seeing the errors and defects in that branch of military surgery, and of studying to remove them. It drew my attention to inflammation in general, and enabled me to make observations which have formed the basis of the present Treatise. That office which I now hold has afforded me the means of extending my pursuits, and of laying this work before the public.

As the object of this book is the improvement of surgery in general, and particularly of that branch of it which is peculiarly directed to the service of the army, I am led by my situation, my duty, and my feelings, to address it, with all humility, to your Majesty.

That your Majesty may long live to enjoy the love and esteem of a happy people, is the fervent wish of

YOUR MAJESTY'S
MOST FAITHFUL SUBJECT,
AND MOST DUTIFUL SERVANT,
JOHN HUNTER.

Leicester Square,
May 20, 1793.

which local disease produces, except that of Mr. John Hunter's *TREATISE ON THE BLOOD, INFLAMMATION, &c.*

That Hunter was pre-eminently fitted to write such a treatise, the following quotation from the advertisement to the English edition will abundantly show:

Mr. Hunter, in the year 1760, went as senior surgeon on the staff to Bellisle and Portugal, and continued abroad in active employment during the war, and there acquired a complete knowledge of *gun-shot wounds*, which can alone be procured by *actual* experience. In the year 1790 he was appointed inspector-general of hospitals, and surgeon-general of the army. Three years after this appointment, having long maturely weighed the important subject of gun-shot wounds, with the effects thereby procured (having now had three and thirty years ample experience) he brought forward his immortal treatise on the blood, inflammation, and *gun-shot* wounds. The expectation of the public was great, nor was it disappointed; for this work was found to answer the exalted reputation of the author. It was not a collection of the sentiments of others, but his own observations. It was wholly original.

It is interesting for Americans to note that a number of the experiments contained in Hunter's "Treatise on the Blood" were performed by one of his American pupils, Dr. Philip Syng Physick of Philadelphia, later known as the "Father of American Surgery." In this treatise, on p. 94, Hunter says: "Many of these experiments were repeated, by my desire, by Dr. Physick, now of Philadelphia, when he acted as house-surgeon at St. George's Hospital, whose accuracy I could depend upon." Hunter was so pleased with Physick that he offered him a share in his business, which, fortunately for this country, he declined.

A complete edition of Hunter's works was issued in London in 1837, in four octavo volumes, illustrated by a volume of plates in quarto, under the supervision of James F. Palmer,²⁰ assisted by Drewry Ottley, Thomas Bell, George B. Babington, and Richard Owen. Palmer himself superintended the publication of the "Lectures on the Principles of Surgery," and on the "Treatise on the Blood, Inflammation, and Gun-shot Wounds"; to Bell, an eminent dentist, was assigned the tract of the "Teeth"; Babington, a physician of wide reputation, took charge of the "Treatise on the Venereal Disease";

²⁰ In vol. I, of Palmer's edition of Hunter's complete works, appears Ottley's admirable "Life of Hunter," by far the best which we possess. It comprises 198 pages. The remainder of this volume contains Hunter's "Lectures on the Principles of Surgery." Vol. II contains the two treatises on the "Teeth," and the "Treatise on the Venereal Disease." Vol. III is a reprint of the "Treatise on Inflammation," comprising 638 pages, and an elaborate general index to the three volumes, consisting of the remaining 38 pages. Nine pages descriptive of the plates then follow, the plates themselves appearing in a separate volume, quarto in size. Vol. IV is a reprint of the "Animal Economy."

In 1861 the scientific works of Hunter were published, in two octavo volumes, under the caption "Essays and Observations on Natural History, Anatomy, Physiology, Psychology, and Geology." These were edited by Professor Richard Owen. Vol. I contains observations on natural history, physiology, palæontology, phytology, and a treatise on animals. Vol. II contains the observations on comparative anatomy.

and Owen edited the papers on "Comparative Anatomy and Physiology," including an account of those published in the Philosophical Transactions. Ottley furnished a biography of Hunter for the first volume, which contains by far the most able and lucid account of him and of his writings that has ever been written. The "Lectures on the Principles of Surgery" were mainly printed from a copy, taken in short hand, by Nathaniel Rumsey, a pupil of Hunter.

In 1842, "A Descriptive and Illustrated Catalogue of the Calculi and other Animal Concretions Contained in the Museum of the Royal College of Surgeons in London," was published. The greater part of this collection, amounting to about six hundred specimens, was formed by Hunter.

DEGREES AND HONORS.

Hunter received numerous testimonials of esteem and appreciation from learned societies at home and abroad, as well as friendly recognition from his own sovereign. In 1767 he was made a Fellow of the Royal Society of London; in 1776, Surgeon Extraordinary to George III; in 1783, a member of the Royal Society of Medicine and of the Royal Academy of Surgery in Paris; in 1786, Deputy Surgeon-General of the army; and in 1789, four years before his death, Surgeon-General and Inspector. The Copley medal of the Royal Society, the highest distinction in its gift, was conferred upon him in 1787, in recognition of the value of his services as an original investigator. The American Philosophical Society, the Royal College of Surgeons of Ireland, the Chirurgico-Physical Society of Edinburgh, and the Royal Society of Sciences and Belles-Lettres of Gottenburg also enrolled him among their members.

PRIVATE LIFE.

Hunter led a busy life. He was one of the most industrious of men, spending, for the furtherance of his great aims, practically all that he made. His brother-in-law, Sir Everard Home, tells us that for the first eleven years of Hunter's practice, 1763-1774, his income never amounted to a thousand pounds a year; and that he always added something to his collection as soon as he had succeeded in collecting fees to the amount of ten guineas. In the year 1778 his income exceeded a thousand pounds; for several years before his death it had increased to five, and at that period was above six thousand pounds.

In 1768 Hunter changed his residence, moving from Golden Square to Jermyn Street, into the house vacated by his brother William. The first part of the "Treatise on the Natural History of the Human Teeth" was published in May, 1771, and two months later he married Anne, elder daughter of Robert Boyne Home, surgeon to Burgoyne's regiment of light horse. She was twenty-nine years old and he was forty-three. They had been engaged many years; but Hunter's financial condition did not permit of an earlier marriage, and it is

stated that he used the proceeds of the above publication to defray the expenses of his wedding. Their married life is said to have been a happy one. Four children were born unto them, only two of whom grew to maturity.

In 1783, Hunter's lease of the house on Jermyn Street came to an end. His collection had grown so rapidly that he sought for more commodious accommodations, and purchased a large house on the east side of Leicester Square, with the ground behind it, and a house on Castle Street (it was No. 13), now part of Charing Cross Road. He continued to reside in Leicester Square until he died, with the exception of the summers, which were still spent at Earl's Court. Between the two houses he erected a building for his museum, on which he expended above three thousand pounds. It was ready for occupancy in April, 1785. Everard Home, William Bell, and a new assistant, André, helped to move the preparations and arrange them in the new building, which was opened to visitors in 1787.

With the exception of an attack of pneumonia in 1759, Hunter enjoyed excellent health during the first forty years of his life. In 1769 he had a severe attack of gout, and another in 1773, accompanied by a spasmodic affection of different parts of his body, eventually involving his heart. From this time his cardiac disturbance was apt to recur after exertion, fatigue, or mental irritation.²¹ In December, 1789, four years before his death, he was suddenly seized with a total loss of memory, lasting for fully half an hour. In the autumn of 1790, and in the spring and autumn of 1791, his attacks of angina became more and more severe; in the beginning of October, 1792, he had one so violent as to almost cause his death.²²

In person Hunter was about the middle stature, measuring five feet two inches in height, uncommonly strong and active, very compactly made, but free from corpulency, and capable of great bodily exertion. His shoulders were high, and his neck short. His eyes and complexion were light, his brows heavy, his cheeks rather high, and, as one of his biographers (Jesse Foot) expresses it, his mouth was somewhat underhung. In a word, his features were rather large, and strongly marked. His hair, in his youth, was inclined to red, but as he advanced in life it became gray, and at length partially white. His countenance was animated, open, and in the latter part of his life deeply impressed with thoughtfulness. When an engraving of him was shown to Lavater, he said, "That man thinks for himself." He required little sleep, often working, with hardly any intermission, for nearly twenty hours out of the twenty-four. He was unassuming in his manners, but rather cold and reserved at times; in his dress he was plain and simple, and not always neat.

²¹ He was accustomed to say that "his life was in the hands of any rascal who chose to annoy and tease him."

²² In addition to the above he had a severe attack of illness in the spring of 1777, and another in 1785, lasting about fifty days.

CLOSING YEARS.

Hunter's final hour came at last—death, sudden and unexpected, overtook him at St. George's Hospital. A special meeting of the governors and of the surgical staff of that institution had been called, to discuss business of importance connected with the admission of pupils and the mode of instructing them. A remark which Hunter made during the discussion was flatly contradicted by one of his colleagues. This disturbed Hunter immeasurably; and, as a consequence, he was seized with a most excruciating attack of angina. He immediately ceased speaking and hurried into an adjoining room, to fight out his pain by himself. His nephew, Dr. Matthew Baillie, followed him from the board-room; he went a few steps, gave a deep groan and fell into the arms of Dr. Robertson, one of the physicians of the hospital who chanced to be present, and expired.

Hunter's brother-in-law and assistant, Everard Home, who was in the hospital at the time, was also summoned. Various attempts were made for upwards of an hour to restore animation, under the hope that the attack might prove to be a fainting fit, such as he had before experienced, but in vain. His body was placed in a sedan chair and conveyed to Leicester-Square, followed by his now vacant carriage.²³

This most distressing event put an end to the business of the meeting. The only notice to be found on the books of that day's proceedings is the following minute:

"Resolved,—That Mr. Hunter's letter to this Board relating to two of the surgeons' pupils, which was received this day, be preserved for future consideration."

An occurrence so sad and so unusual called forth a widespread sympathy, and created a profound sensation wherever Hunter's name and fame were known and appreciated. In the language of Professor Gross, ("John Hunter and His Pupils," pp. 26 and 27):

Like Cæsar, Hunter was murdered by his friends, not in the senate chamber, but in the consultation room of a hospital which had so long been the recipient of his services, of which he was the chief ornament, and which should have overlooked his infirmities, some of them inherent in his nature and others the result of long-continued overwork of mind and body.

²³ Mrs. Hunter survived her husband twenty-seven years, dying January 7, 1821, aged seventy-nine. According to Ottley, "she was an agreeable, clever, and handsome woman, a little of the *bas bleu*, and rather fond of gay society, a taste which occasionally interfered with her husband's more philosophical pursuits." She wrote the Shepherd's Song, "My Mother Bids Me Bind My Hair," immortalized by the setting which Haydn gave it; she also wrote the words for Haydn's "Creation." In her latter years she published a small volume of poems, which possess considerable merit as a light effort. She was universally beloved and esteemed, retaining her wit and beauty to the end of her days. The Hunterian orator of 1821 paid to her memory this heavy compliment—that "she had sustained an honourable widowhood, estimable for talents of her own, and venerable as the relict of her illustrious husband."

Even Jesse Foot was moved to eulogistic expression when he wrote the following ("Life of John Hunter," p. 282):

On being told of this event, on the same day, I recollected seeing the bay stallions returning, through Piccadilly, home, without their master; and this circumstance introduced to my reflection the sympathy which Virgil has attributed to the war-horse of young Pallas in his funeral procession—

*Post bellator Equus, positus insignibus Æthon
It lachrymans.*

Hunter's death occurred on Wednesday, October 16, 1793, in the sixty-fifth year of his age. On the following Tuesday (October 22) his body was interred²⁴ in one of the public vaults of the church of St. Martin's-in-the-Fields, the obsequies being attended only by the family and a few intimate medical friends.

The autopsy,²⁵ performed by Everard Home and Dr. Matthew Baillie, amply confirmed the diagnosis of his friend and pupil, Dr. Jenner. It revealed the existence of ossification of the mitral valves of the heart and dilatation of the aorta, with thickening of its valves and degeneration of its coats. The coronary arteries were converted into long, rigid tubes. The heart itself was uncommonly small.²⁶

That Hunter wished an autopsy to be performed upon him, the subjoined foot-note on p. 132, of Ottley's "Life," would indicate:

It has been supposed by some that Hunter had the same antipathy to the scalpel of the anatomist as was felt by his brother; but this was by no means the case; on the contrary, he always spoke of it as a matter of course, and used, in the strongest language, to express his condemnation of those who should neglect to examine his body and preserve his heart. It is to be regretted that no relic of this sort has been preserved."

Commenting upon Hunter's death, Ottley, on the following page (p. 133), adds:

Thus, in his sixty-fifth year, died John Hunter, celebrated alike as a surgeon and as a naturalist; in neither of which capacities has he had many equals,—in his combined character, none.

²⁴ The burial took place at quarter past four in the afternoon, as the following entry in the sexton's old register-book at St. Martin's Church would indicate. The statement, however, that Hunter died of apoplexy, is inaccurate.

"1793, Oct. 22, John Hunter, Esq., Leicester Square, No. 3 vault, 6l. 10s. 0d.—no candles, ¼ past 4. Apoplexy."

²⁵ For a detailed account of the post mortem appearances, the thoughtful reader is invited to turn to pp. lxii, to lxxv, of the Life by Home, prefixed to the "Treatise on Inflammation"; or to an article entitled "Angina Pectoris and Allied States," by Professor Gairdner, M. D., in vol. IV, of Reynolds' "System of Medicine," p. 560 *et seq.*

²⁶ I am inclined to believe that the aneurismal dilatation of Hunter's aorta, and the other pathological conditions noted above, which caused his death, were largely due to an attack of syphilis which he had had in early manhood as the result of his inoculating himself on the glans and prepuce, in May, 1767, with secretion from what was probably a concealed urethral chancre, mistaking it for gonorrhœal discharge. Then, too, he was subjected to other perturbing influences productive of arteriosclerosis—worry, overwork, financial embarrassment, loss of sleep, and a hasty temper.

MEMOIRS OF HUNTER.

Memoirs of Hunter were published soon after his death by his brother-in-law, Everard Home, Jesse Foot, Surgeon, and Dr. Joseph Adams, an eminent English medical scholar.

The "Life" by Home was prefixed to the first edition of Hunter's "Treatise on Inflammation," but was omitted in the subsequent issues. It is a splendid account of the life and labors, professional and private, of this justly celebrated British surgeon, "the first anatomist and the first surgeon in the world," as many talked of him in the later part of his brilliant and eventful career.²⁷

In the same year, 1794, Jesse Foot published his "Life of John Hunter," an octavo volume of 287 pages. This memoir was not well received by the profession. Ottley states that some of Hunter's enemies paid Foot four hundred pounds for writing it. The work is characterized by Professor Gross as "a scurrilous attempt to depreciate the character of Hunter as a scientific man, and abounds, as might be supposed, in flagrant misstatements and wilful misrepresentations." "If the author had set out," he continues, "with a determination to gain an ignominious immortality, he could not have succeeded better."

Despite the numerous aspersions which have been cast upon Jesse Foot's book, I find at least some little good in it.

His description of Hunter's habits of work, coming first-hand from one who knew him personally, is one of the best which we have (p. 285):

I believe John Hunter to have been one of the most industrious of men. The way in which his time was devoted,—before he obtained the public appointments,—was, as follows:—He rose very early in the morning, and went immediately into the dissecting room,—where he sometimes dissected, and gave directions concerning, what he would have done, in the course of the day. After breakfast, he attended to those patients who came to his house. At eleven he went abroad; and was employed in visiting patients,—attending at the hospital,—and when the occasion called for it, in opening dead bodies. He eat very hearty at his dinner,—and rarely drank more, than a glass of wine, and sometimes not that. In the evening, he was engaged in reading his lectures, and writing down observations, which he had made through the day,—or preparing, for the next coming publication. He seldom retired to rest till twelve, or one o'clock.

In 1817 a meritorious work appeared, entitled "Memoirs of the Life and Doctrines of the late John Hunter, Esq., founder of the Hunterian Museum at the Royal College of Surgeons in London," written by Dr. Joseph Adams. The portrait prefixed to this work is from a bust by Bacon, in the execution of which he was assisted by a cast taken during life. In the following year a second edition was called for. The portrait in this edition is from a bust by Flaxman, in the execution of which he also was assisted by a cast taken during life.

²⁷ He was the greatest man in the combined character of physiologist and surgeon that the whole annals of medicine can furnish (Lawrence).

In 1833, Parkinson's "Hunterian Reminiscences" were published.²⁸

In 1837 appeared the excellent memoir by Drewry Ottley, prepared for Palmer's edition of Hunter's complete works. This is by far the most able, full and impartial memoir that we have of him. The portrait of Hunter is identical with that in the second (1818) edition of Adams' "Memoirs."

A good memoir of Hunter is to be found in Vol. XXII, of the Naturalist's Library, edited by Sir William Jardine and published in 1854. In 1881, there was published a small octavo volume by Professor Samuel D. Gross, of Philadelphia, entitled "John Hunter and His Pupils." In his opening paragraph he says:

All intelligent readers of biography are more or less familiar with the labors and writings of John Hunter, his marvellous genius, and his vast contributions to science. In the medical profession his name is, and always will be, a household word throughout the civilized world; it is spoken with respect and reverence in every college amphitheatre, and is deeply engraved upon the mind of every student of surgery. Nevertheless there are, it may safely be asserted, many points of interest in his life, and many traits of character, which have escaped our memory, or which have never been so thoroughly impressed upon our attention as to enable us to appreciate them at their full value.

²⁸ The following is a copy of the title-page of this comely volume, now excessively rare and extremely difficult to obtain:

HUNTERIAN REMINISCENCES;
Being the Substance of a
COURSE OF LECTURES
on the
PRINCIPLES AND PRACTICE OF SURGERY,
Delivered by the Late
MR. JOHN HUNTER,
IN THE YEAR 1785:
TAKEN IN SHORT-HAND, AND AFTERWARDS FAIRLY
TRANSCRIBED, BY
THE LATE MR. JAMES PARKINSON,
Author of "Organic Remains of a Former World," &c.

Edited By His Son,
J. W. K. PARKINSON,
Fellow of the Royal College of Surgeons, in London,
By whom are appended
ILLUSTRATIVE NOTES.

LONDON:
SHERWOOD, GILBERT, AND PIPER, PATERNOSTER ROW.

1833.

The dedication is interesting, and calls to mind many historical associations. It reads, as follows:

TO
MR. WILLIAM CLIFT,
Formerly the Zealous and Diligent Assistant of the Late
MR. JOHN HUNTER,
Now the Able Conservator and Intelligent Illustrator
of the
HUNTERIAN MUSEUM,
THIS WORK IS INSCRIBED,
by
THE EDITOR.

In 1893, George Mather, a celebrated British physician, wrote an engaging volume entitled "Two Great Scotsmen—William and John Hunter," in which is contained a most fascinating record of John Hunter's life and labors. In the "Masters of Medicine" series, there is an admirable little book entitled "John Hunter, Man of Science and Surgeon," 1897, by Stephen Paget. Notices, more or less elaborate, of Hunter have also appeared in the various orations which have been delivered, since 1814, in commemoration of him by the president and fellows of the Royal College of Surgeons of England. The brief eulogy by the president, Sir William Mac Cormac, at the centenary festival of the Royal College of Surgeons held in London on Thursday, July 26, 1900, is the most beautiful tribute to Hunter that I know. He says:

Of John Hunter (1728-1793) no detailed mention is required here. His memory and his methods continue a living influence amongst us. He made our Surgery a science, and has given to us in our Museum an imperishable memorial of his industry. In it are illustrated those marvellous powers of observation which had never before been equalled, and will never in all probability be surpassed. So long as Surgery continues, Hunter's influence must be felt. It is witnessed in the creation of so many distinguished disciples imbued with his principles and able to expound his doctrines. He embodies and represents the glory of our Science, our College, and our Country.

MEMORIALS TO HUNTER.

The casual observer will find much to remind him that John Hunter lived among men. Of the various portraits that are extant of him, that by Sir Joshua Reynolds, painted in 1787, is by far the best. It represents him as sitting in a chair in deep thought, with a pen in one hand and the other supporting his chin. Three of the folio volumes of MSS., burned thirty-six years later by Sir Everard Home, are placed at his side. Other things around him, in addition to the manuscripts, are the jars containing preparations, and the dangling feet of the Irish giant's skeleton, the latter said to have cost Hunter the extravagant sum of £500. From this portrait by Reynolds an admirable engraving was made by Sharp.

As a frontispiece to Hunter's "Essays and Observations" there is a good likeness of him, after a medallion taken in 1791. Another favorite likeness is a pencil drawing taken by Sir Nathaniel Holland in 1793, the year of Hunter's death. After Hunter's death a bust of him was made by Flaxman, in the execution of which he was assisted by a cast taken during life.

The Hunterian museum, purchased by the British Government and placed in custody of the Royal College of Surgeons of England, is another mighty reminder of Hunter and his indefatigable industry. Hunter's executors, Sir Everard Home and Dr. Matthew Baillie, on June 13, 1799, sold the museum to the Government for £15,000. It cost £70,000. The trustees held it for six years, but Mrs. Hunter's financial needs were pressing, and for this reason they urged the sale. The original collection was estimated by Prof. Charles Stewart and Timothy Holmes to consist of 13,682 specimens, the

largest number ever gotten together by one man, distributed under the following heads:

I. PHYSIOLOGICAL DEPARTMENT, OR NORMAL STRUCTURES.	
1. Physiological preparations in spirit,.....	3,745
2. Osteological preparations,.....	965
3. Dry preparations,.....	617
4. Zoological preparations,.....	1,968
5. Fossils:—	
a. Vertebrate,	1,215
b. Invertebrate,	2,202
c. Plants,	292
II. PATHOLOGICAL DEPARTMENT, OR ABNORMAL STRUCTURES.	
1. Preparations in spirit,.....	1,084
2. Dry preparations (including bones),.....	625
3. Calculi and concretions,.....	536
4. Monsters and malformations.....	218
III. Microscopic preparations,	215

Catalogues of the Hunterian Museum, comprising ten quarto volumes, were prepared many years ago (1833-1856) by Professor Richard Owen and Mr., later Sir James, Paget, the latter having charge of the pathological specimens. The first curator, or, as he is styled in England, conservator, of the museum was William Clift, Hunter's last assistant.

In the year 1813 Dr. Matthew Baillie and Sir Everard Home, executors of John Hunter, "being desirous of showing a lasting mark of respect to the memory of the late Mr. John Hunter," gave to the Royal College of Surgeons of England the sum of £1684 4s. 4d., for the endowment of an annual oration, to be called the Hunterian oration, and to be delivered in the theatre of the college on Hunter's birthday. The first Hunterian oration was delivered on February 14, 1814, Sir Everard Home being the orator. In 1853 it was decided that the oration should in future be delivered biennially instead of annually. The next Hunterian oration will be delivered by Sir Rickman Godlee,²⁹ president of the Col-

²⁹ The following reference thereto appeared on p. 146, of *T. P.'s Weekly*, of date January 31, 1913.
"The Hunterian Festival, which is held biennially, takes place on February 14 at the Royal College of Surgeons. The oration will be delivered by the president, Sir Rickman J. Godlee, in the afternoon, and the customary banquet will be held in the library of the college in the evening."

³⁰ At the same time I received the subjoined letter:
Royal College of Surgeons of England,
Lincoln's Inn Fields,
London, W. C.
2d day of December, 1912.

Dear Sir:—I am desired by the president, Sir Rickman Godlee, to send you the enclosed particulars with reference to the Hunterian oration.
Each oration is called simply the Hunterian oration, and no other title is ever adopted.

Dr. Frank Buckland presented to the college a photograph of John Hunter's coffin, taken when it was removed from St. Martin's-in-the-Fields, and this is in the library of the college. There are, however, no duplicates, nor have we any photographs

lege, on Friday, February 14, of the present year. To him I am indebted for the complete list of Hunterian orators:³⁰

1814. Sir Everard Home, Bart.	1853. Bransby Blake Cooper.
1815. Sir William Blizard, Knt.	1855. Joseph Hodgson.
1816. Henry Cline.	1857. Thomas Wormald.
1817. William Norris.	1859. John Bishop.
1818. Sir David Dundas, Bart.	1861. William Coulson.
1819. John Abernethy.	1863. George Gulliver.
1820. Sir Anthony Carlisle, Knt.	1865. Richard Partridge.
1821. Thomas Chevalier.	1867. John Hilton.
1822. Sir Everard Home, Bart.	1869. Richard Quain.
1823. Sir William Blizard, Knt.	1871. Sir William Fergusson, Bart.
1824. Henry Cline.	1873. Henry Hancock.
1825. William Norris.	1875. Frederick Le Gros Clark.
1826. Sir Anthony Carlisle, Knt.	1877. Sir James Paget, Bart.
1827. Honoratus Leigh Thomas.	1879. George Murray Humphry.
1828. Sir William Blizard, Knt.	1881. Luther Holden.
1829. John Painter Vincent.	1883. Sir Thomas Spencer Wells, Bart.
1830. George James Guthrie.	1885. John Marshall.
1831. Anthony White.	1887. William Scovell Savory.
1832. Samuel Cooper.	1889. Henry Power.
1833. John Howship.	1891. Jonathan Hutchinson.
1834. William Lawrence.	1893. Thomas Bryant.
1837. Sir Benjamin Collins Brodie, Bart.	1895. John Whitaker Hulke.
1838. Benjamin Travers.	1897. Christopher Heath.
1839. Edward Stanley.	1899. Sir William MacCormac, Bart.
1840. Joseph Henry Green.	1901. Nottidge Charles Macnamara.
1841. Thomas Callaway.	1903. Sir Henry Greenway Howse, Knt.
1842. George Gisborne Babington.	1905. John Tweedy.
1843. James Moncrieff Arnott.	1907. Henry Trentham Butlin.
1844. John Flint South.	1909. Henry Morris.
1846. William Lawrence.	1911. Edmund Owen.
1847. Joseph Henry Green.	1913. Sir Rickman John Godlee, Bart.
1848. Richard Dugard Grainger.	
1849. Cæsar Henry Hawkins.	
1850. Frederic Carpenter Skey.	
1852. James Luke.	

In 1859 the remains of John Hunter were removed from St. Martin's-in-the-Fields and reinterred in Westminster Abbey, largely through the efforts of Frank Buckland, the eminent naturalist.³¹ For sixteen days, with but one assistant, he

of the tomb in Westminster Abbey; but the president is pleased to send you the enclosed copy of the inscription on the tomb.
The president also desires me to thank you for the two pamphlets which you have kindly sent to him.
Yours faithfully,
(Signed) S. FORREST COWELL,
Secretary.

DR. C. W. G. ROHRER.

³¹ The beginning of the story of the discovery, on February 22, 1859, of the remains of John Hunter in the vaults of St. Martin's-in-the-Fields, is also of absorbing interest, and I shall here give it in Mr. Buckland's own words, as related by him on pp. 215-218, of his "Curiosities of Natural History," Fourth Series:

"In the month of January, 1859, when sitting in the mess-room of the 2d Life Guards, at Windsor, looking over the advertisement sheet of the 'Times,' the following caught my attention:—

"'ST. MARTIN'S-in-the-FIELDS—CHURCH VAULTS AND CATACOMBS—ORDER in COUNCIL—NOTICE. Any person or persons having the remains of relatives or friends deposited in any of the vaults under the church, or in any of the catacombs under the churchyard, situate at the north-east corner of Trafalgar Square, are hereby informed that they may, if they so desire,

searched the vaults of St. Martin's, before finding Hunter's coffin. It was well preserved, bearing upon it, besides the brass name plate, Hunter's arms—a hand with an arrow in it, and the three horns of the hunter. The happy culmination of this extraordinary labor of Mr. Buckland, this "chivalrous devotion to the relics of a great man," can best be described in his own words.³²

After a time all the coffins were removed away from the vault but five; two lay side by side upon the floor, and three one over the other in a corner of the vault; and I could see the names on all these coffins except two: my chance was now therefore limited to these two coffins.

The total number of coffins in No. 3 vault was over two hundred. The total number of coffins removed was three thousand two hundred and sixty. This will give some idea of the task that I had undertaken and had now nearly finished. If one of these coffins therefore was not John Hunter's, all our labours would have been in vain. The workmen stood at the head and foot of the uppermost coffin of the three, and slowly moved it away that I might see the name upon that immediately below it. As it moved slowly off, I discerned first the letter J, then the O, and at last the whole word John. My anxiety was now at its height, and quickly running to one end, Mr. Burstall at the other, we moved the coffin away. At last I got it completely off, and to my intense delight read upon the brass plate the following inscription:—

JOHN HUNTER,
Esq.,
DIED 16TH OCTR.,
1793,
Aged 64 Years.

The Hunters' arms, viz., a hand with an arrow on it, also the three horns of the hunter, were upon the plate.

Lest there should be any subsequent doubt upon the identity of this coffin, a photograph was taken of it by Mr. Soame, which I have presented to the Royal College of Surgeons.

On March 28, re-interment was made in Westminster Abbey with impressive ceremonies.³³ On the following day, March

remove the same before the 1st day of February 1859; after which date, all coffins remaining in the said vaults or catacombs will be reinterred in the same place, and finally built and closed up in accordance with the said Order in Council, and cannot afterwards be inspected on any pretence whatever.

"BENJAMIN LATCHFORD, } Churchwardens of the said
CHARLES H. PETTER, } Parish.

"All communications to be made in writing, addressed to us at the Vestry House, Adelaide Place, W. C."

"Why, surely John Hunter is buried in this church, was the thought that immediately struck my mind: his remains ought certainly to be looked after; but who is to do it? I will try to rescue his remains. If I fail there will be no harm done."

³² "Curiosities of Natural History," Fourth Series, pp. 225 and 226.

³³ I take pleasure in giving the following brief account of the funeral rites at the re-interment of the remains of Hunter, because such information is not readily accessible to the reader:

Very great interest had been excited among the profession when the intention of the Council of the College to undertake the pious duty of the removal to the Abbey had been made public, and a very numerous assemblage collected there early in the afternoon of the 28th of March; and it having been intimated that the choral service would be suited to the solemnity, which would take place immediately afterwards, the choir was crowded with

29, 1859, an address was delivered by Joseph Henry Green, president of the Royal College of Surgeons of England, urg-

medical men, of whom many had come from the country to testify their respect for John Hunter's memory.

The Musical Service consisted of—

Single Chant to Psalms.....*Turle*.
"Magnificat" and "Nunc dimittis".....*Farrant*.

ANTHEM.

"When the ear heard him." }.....*Handel*.
"His body is buried in peace." }

Soon after four o'clock the procession, headed by the vergers, passed from the Jerusalem Chamber into the Abbey, arranged in the following order:—

The Dean of Westminster. W. Hunter Baillie, Esq.
Frank T. Buckland, Esq. Richard Owen, Esq.
The President of the Royal Col- Earl of Ducie.
lege of Physicians.

The President of the Royal College of Surgeons of England.

The Vice-Presidents and

The Council of the Royal College of Surgeons.

The Censors of the Royal College of Physicians.

The Master of the Society of Apothecaries of London.

The Director-General of the The President of the Linnæan
Navy Medical Department. Society.

And other Members of the Medical Profession.

The procession having reached Abbot Islip's Chapel, and the coffin, uncovered and placed on a bier, having been raised on shoulders, proceeded round St. Edward's Chapel into the nave, the Dead March in "Samson" being played by Mr. Turle, and continued till the grave was reached, in which the

REMAINS OF JOHN HUNTER

were lowered whilst the pealing organ poured forth Handel's grand and sublime chorus, well suited to this memorable occasion—

HIS BODY IS BURIED IN PEACE, BUT HIS NAME LIVETH
EVERMORE.*

*A very handsome ornamental brass tablet now covers the tomb, upon which is the following inscription, written by John Flint South, the well-known author of *Memorials of the Craft of Surgery*:—

"O Lord, how manifold are Thy Works."

Beneath
are deposited the remains of
JOHN HUNTER.

Born at Long Calderwood, Lanarkshire, N. B.,
on the 13th of February, 1728.

Died in London on the 16th of October, 1793.

His Remains were removed from the Church
of St. Martin's-in-the-Fields to this Abbey
on the 28th of March, 1859.

The Royal College of Surgeons of England have placed this Tablet over the grave of Hunter, to record their admiration of his genius, as a gifted interpreter of Divine Power and Wisdom at work in the Laws of Organic Life, and their grateful veneration for his services to mankind as the founder of Scientific Surgery.

"In wisdom hast Thou made them all."—Ps.civ. 24.

ing the erection of a statue to Hunter. Mainly through the efforts of John Flint South, one of the vice-presidents of the college, the sum of £1172 17s. 1d. was promptly raised for that object. The work was intrusted to Mr. Weekes, the eminent sculptor, who produced an admirable likeness which was completed in 1864, and now graces the first room on the lower floor of the museum of the college.

On May 29, 1886, a statue of John Hunter was unveiled in the University museum, at Oxford, England, on which occasion Sir James Paget was one of the speakers. A bust of Hunter, along with that of Newton, of Hogarth, and of Reynolds, occupies one of the four corners of Leicester Square, London; and there is a window to his memory in the church of St. Mary Abbott's, Kensington.

Another constant reminder of John Hunter and his unwearyed labors is the Hunterian laboratory connected with the medical school of *this* university—the leading institution of its kind on the Western Hemisphere. Founded in 1906, it stands to-day a pioneer in the diffusion of such knowledge as Hunter endeavored to convey. Truly, "its line has gone out to the ends of the earth;" and it not only reflects lasting credit upon those who nurtured it and gave it birth, but also bears with dignity an appellation which can justly be applied to it; namely, "the greatest of all memorials to John Hunter."

SUMMARY OF LIFE WORK.³⁴

John Hunter not only laid the foundations of scientific surgery, but his name is also indelibly associated with the rise and progress of histology, physiology, and comparative anatomy.

In the language of Professor Gross:

He was not only a great surgeon, a wise physician, and a great anatomist and physiologist, human and comparative, but, above all, he was a philosopher whose mental grasp embraced the whole range of nature's works, from the humble structure to the most complex and the most lofty. He was emphatically the Newton of the medical profession, and what Pope said of that great philosopher may, by paraphrase, be said with equal force and truth of Hunter:

"Nature and Nature's laws lay hid in night;
God said 'Let Hunter be,' and all was light."

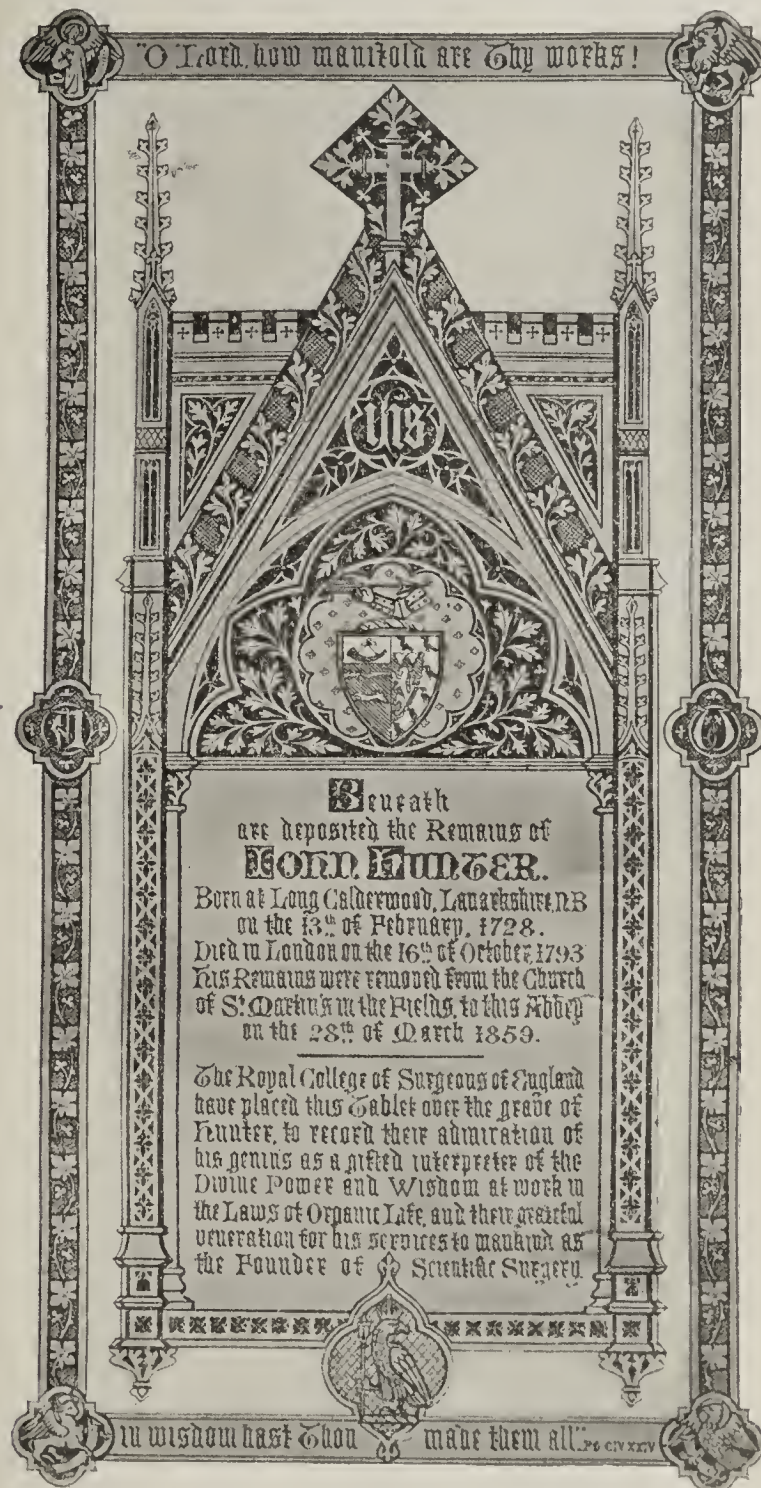
Hunter is peerless in the history of British surgery; and after the lapse of nearly a century the profession turns to his memory with increased reverence for his transcendent genius, his matchless ability, and his unequalled services. To say that he was simply the founder of scientific surgery would fall far short of his great deserts; to do him full justice we must add that he was the father also of scientific zoology and of comparative physiology.

³⁴ British surgeon, anatomist and physiologist. First to discover the system of vessels known as lymphatics, although the function of these vessels was suggested by his brother, William Hunter. His studies of tendons laid the foundation for the operation for the cure of club feet. His experiments to determine the blood-supply for the growing antler of a deer led to the discovery of the "collateral circulation of the blood"—one of the most important discoveries in surgery. This led directly to his invention of the "Hunterian" operation for aneurism, an operation still in use, and which has made the name of Hunter immortal in the annals of surgery (Henry Smith Williams).

It is interesting to record that James Jackson, Jr., M. D., of pious memory, in a letter to his father, is loud in his praise of Hunter and his work, as the following extract will show:³⁵

London, September 28, 1832.

Would you were here, my dear father, to enjoy with me the study of John Hunter's works, and to kindle with me in my admiration of his genius; the elevation and extent of which I



COPY OF THE INSCRIPTION ON JOHN HUNTER'S TOMB IN WESTMINSTER ABBEY.

know not even now; nor does any man living, though my conceptions of his vast and comprehensive mind have been greatly elevated within the last fortnight. His museum is intelligible to no one in its full extent. The materials there collected and arranged, are often indicative of peculiar ideas, which are lost to the world for want of their great interpreter.

³⁵ Memoir of James Jackson, Jr., M. D., p. 160.

For more than forty years Hunter toiled as never man toiled; and yet, so it is stated, his doctrines were not well received by his contemporaries. Some were incited by prejudice, some by envy and jealousy, whilst still others were impelled by a spirit of indifference. Is it any wonder, then, that he should have become discouraged at times? "The few good things I have been able to do," he was heard to say, "have been accomplished with the greatest difficulty, and encountered the greatest opposition."

His labors increased with his years and with his honors; and when the end came, sudden though it was, it found him assiduously engaged in those pursuits which had been the joy and the delight of his life. He pursued studies in every department of natural history and surgery, and added luster to them all. His "mind was like a bee-hive"—full of industry, method, and the laying-up of stores for future use; and whatever he touched he adorned. Hunter had a high opinion of putting one's thoughts into writing. "It resembles," he said, "a tradesman taking stock, without which he never knows what he possesses or in what he is deficient." The infinite variety and wide range of his mental qualifications, is shown in a chronological list of his works and papers, to be found in Ottley's "Life of Hunter" (pp. 189-192).

So far as a bank account was concerned, John Hunter died a poor man; yet who is there among you who would call him poor? His name comes down to us as one of the great figures of the eighteenth century—a century famous for a wonderfully rich harvest of discovery in anatomy and physiology, in medicine and surgery. The mystery, however, is solved when we remember that he rose regularly at four o'clock in the morning, and seldom retired before twelve o'clock at night. The compliment which Cecil paid to Sir Walter Raleigh was equally deserved by Hunter: "I know he can labor terribly." His mind was incessantly in his work.³⁸

³⁸ The following is a summary with the ages and the dates, of the chief events of his life (after Professor Owen, "The Scientific Works of John Hunter," vol. ii, pp. 492, 493. Sir James Paget, in the Hunterian oration for 1877, pp. 37 and 38, also gives a fine calendar of the chief events of Hunter's life):

Age.	Year.	Event.
	1728	Birth, 13th or 14th of February, at Long Calderwood, Kilbride, near Glasgow.
20	1748	Migration to London to his brother, Dr. Wm. Hunter.
25	1753	Entered as "Gentleman Commoner" at St. Mary's, Oxford.
28	1756	House-surgeon at St. George's Hospital, London.
29	1757	Prosecutor and Demonstrator in Dr. Wm. Hunter's Theatre of Anatomy, in Great Windmill Street.
33	1761	As Surgeon in the Army, accompanied the Expedition to Belleisle.
35	1763	Returned from Portugal to London.
38	1766	Communicated his first Paper, printed in the Transactions of the Royal Society, entitled "Anatomical Description of an Amphibious Bipes."
39	1767	Elected Fellow of the Royal Society of London.
40	1768	Became "Member of the Corporation of Surgeons."

Surgery of to-day is immensely indebted to Hunter.³⁷ His constant saying was: "We are but beginning to learn our profession." Dead though he has been for an hundred and twenty years, yet the principles which he taught and the foundations which he laid have become the woof and warp of the surgical fabric of the present day. The ever-widening circle of his influence still abides.

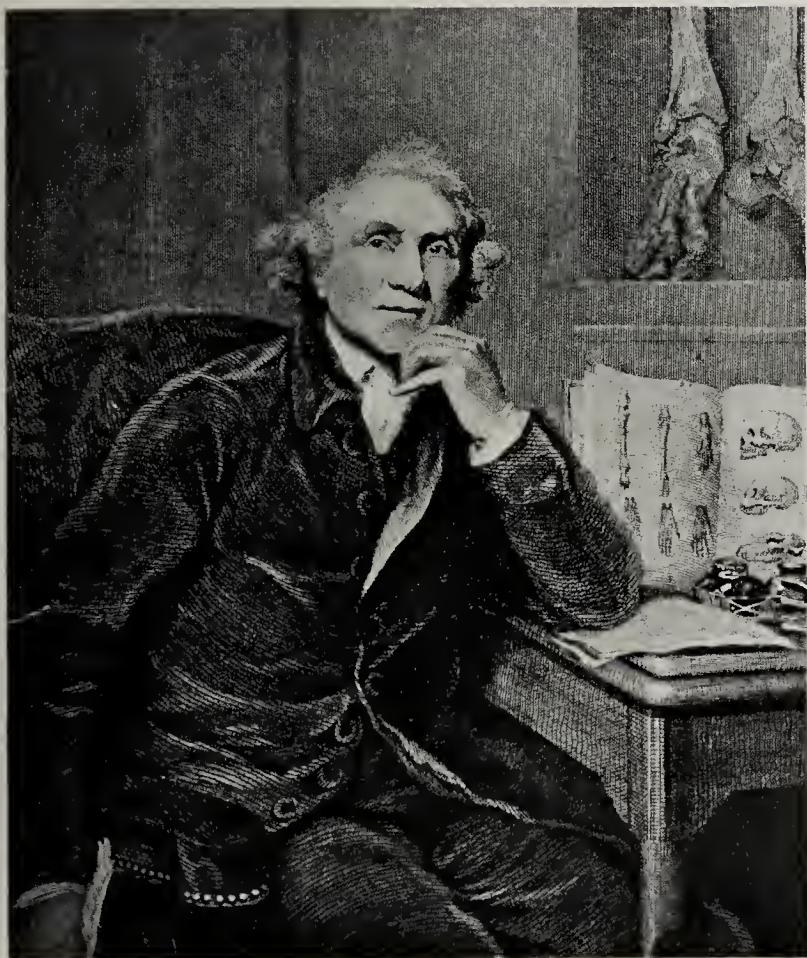
To quote again from Professor Gross:

The lesson of the life of such a man, in every respect so grand and colossal, so powerful and majestic in intellect, and so indissolubly associated with the scientific history of his age and country, is full of instruction, not only to the members of our own profession, but to men in every avenue and pursuit in life. His example of industry and of steady, persistent effort in the cause of human progress reflects the highest credit upon his character, and is worthy of the imitation of every student ambitious of distinction and usefulness. Nowhere, either in ancient or modern times, can there be found a nobler pattern for the formation of a truly scientific career. Commencing life as an erratic, hesitating youth, undecided what to do, or whither to turn, without any promise or definite aim, a source of constant annoyance to his

Age.	Year.	Event.
41	1769	Elected Surgeon to St. George's Hospital: had his first attack of the gout.
42	1770	Jenner became Hunter's House-pupil.
43	1771	Married Miss Home. Published his "Treatise on the Natural History and Diseases of the Human Teeth."
44	1772	Communicated his Paper "On the Torpedo" to the Royal Society. Mr. (afterwards Sir Everard) Home, his wife's brother, became his pupil.
45	1773	His first attack of "Angina pectoris."
46	1774	Gave his first Course of Lectures "On the Principles of Surgery."
48	1776	Appointed Surgeon Extraordinary to His Majesty. Mr. Wm. Bell became Hunter's assistant.
55	1783	Purchased the lease of the house No. 29 Leicester Square, and the ground extending to and including a house in Castle Street, and began to build his Museum on the intervening space.
57	1785	Museum completed, and arrangement of the Preparations begun.
58	1786	Published his "Observations on the Animal Economy," and his work "On the Venereal Disease." Made Dep. Surgeon-General to the Army.
59	1787	Preparations arranged in the Museum, which was opened to Visitors.
61	1789	Mr. Wm. Bell left Hunter for an appointment in Sumatra, where he died in 1792.
64	1792	The printing of the work "On the Blood and Inflammation," was commenced. Mr. Wm. Clift was articulated as an "apprentice" to John Hunter.
65	1793	Died suddenly, October 16th, at St. George's Hospital: was buried in St. Martin's Church.
	1859	Was re-interred, March 28th, in Westminster Abbey.

³⁷ In "Leisure Hour," No. 385, May 12, 1865, Frank Buckland wrote:

Without slighting the labours of other great surgeons and anatomists, it may be confidently affirmed that there is not a man, woman, or child among us who, when struck by the sting of disease, and receiving relief from the art of medicine, does not directly or indirectly receive relief to his suffering from the discoveries of John Hunter.



JOHN HUNTER. ENGRAVING OF REYNOLDS' PORTRAIT.



DR. WILLIAM HUNTER, HUNTER'S BROTHER AND FIRST TEACHER IN ANATOMY.



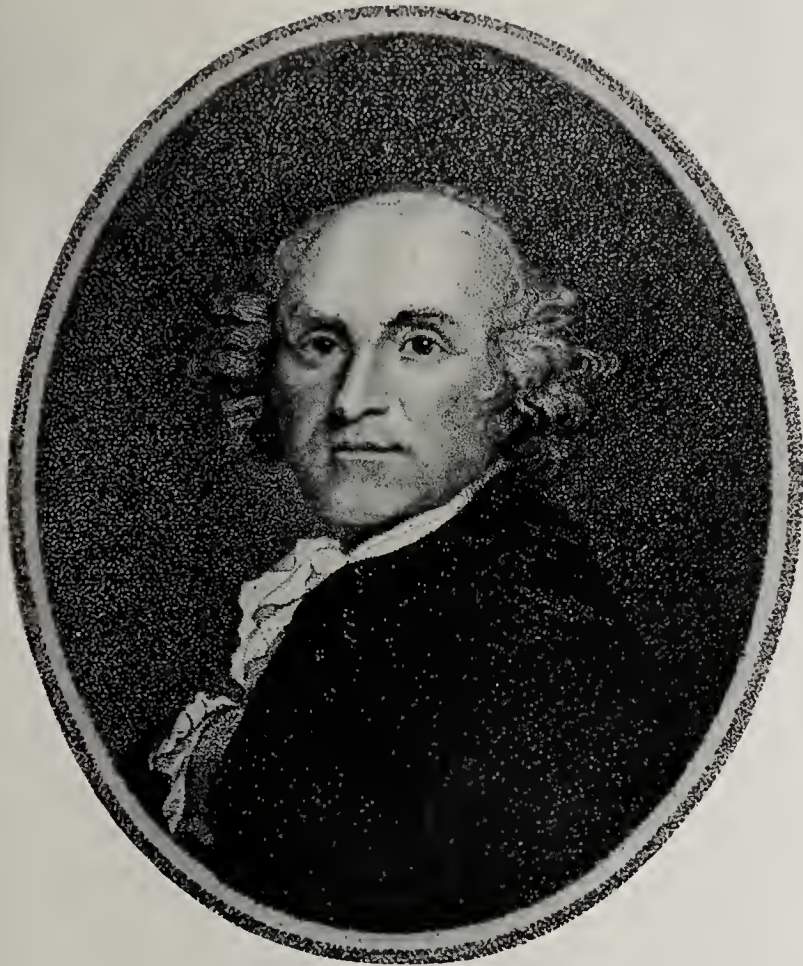
LONG CALDERWOOD.

LONG CALDERWOOD, THE BIRTHPLACE OF HUNTER.

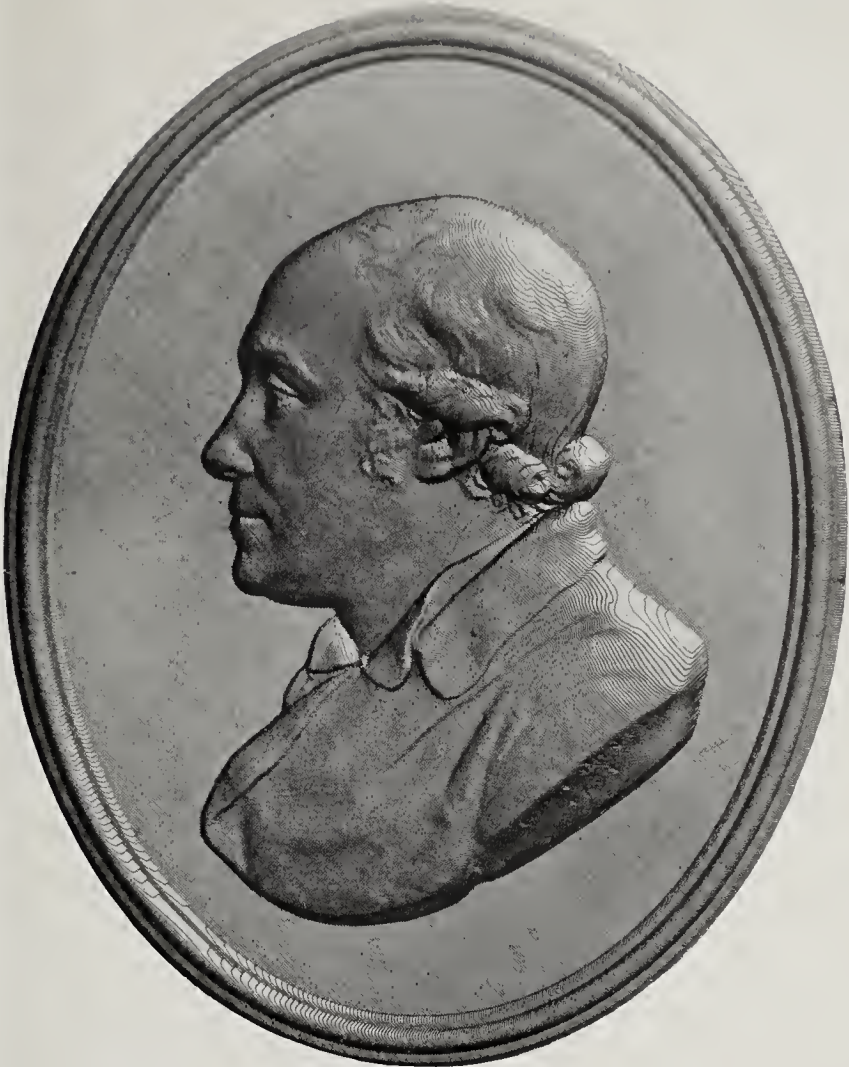


"THE DISSECTING ROOM." By ROWLANDSON.
The figure standing up above the rest is William Hunter; his brother John is on his right-hand side, and Matthew Baillie is the next figure to William Hunter on the left; Cruikshank is seated at the extreme left of the picture, and Monro is working on the side of the table at the bottom.

WM. HUNTER'S DISSECTING-ROOM.



JOHN HUNTER. AFTER JOSI, SCULPTOR.



JOHN HUNTER. AFTER A MEDALLION TAKEN IN 1791.



JOHN HUNTER. PENCIL DRAWING BY HOLLAND.



JOHN HUNTER'S BOOKPLATE WITH ARMORIAL BEARINGS AND
MRS. HUNTER'S BOOKPLATE WITH HER MONOGRAM.

family and of disappointment to his friends, he became eventually one of the most illustrious men in all Europe, leaving behind him imperishable monuments of patient research, of vast genius, and of wonderful philosophical acumen, destined to grow brighter and more stately as the ages roll on, and as men become more and more appreciative of man's work and of man's intellectual powers.

Hunter, to use Dante's phrase, followed his star; and in finding the good that he wished for humanity, found, along with it, name and fame.

His death though precipitate, and in a measure unexpected, was doubtless as he would have wished it to be. He was thereby mercifully delivered from those "cold gradations of decay"—that time in life when old age creeps on apace, and the hands tremble and the eyes grow dim.

Thus ended a career of almost unexampled industry and usefulness; a life abounding in zeal and good deeds, which made the world wiser and better. So we shall leave him—beloved during life, honored at death, secure in his fame; sentiments most beautifully expressed in the following verses written by Mrs. Hunter,⁸⁸ and originally intended for the inscription upon her husband's grave-stone:

Here rests in awful silence, cold and still,
One whom no common sparks of genius fired;
Whose reach of thought Nature alone could fill,
Whose deep research the love of Truth inspired.

Hunter! if years of toil and watchful care,
If the vast labours of a powerful mind
To soothe the ills humanity must share,
Deserve the grateful plaudits of mankind,—
Then be each human weakness buried here
Envy would raise to dim a name so bright:
Those specks which in the orb of day appear
Take nothing from his warm and welcome light.

Acknowledgment is hereby gratefully made to the president of this society, Dr. Henry Barton Jacobs, for much valuable assistance and kindly encouragement so cheerfully given; to its secretary, Dr. Thomas B. Fletcher; to Dr. George H. Whipple, of the Hunterian laboratory; to Sir Rickman Godlee, president of the Royal College of Surgeons of England; and last, but by no means least, to my photographer, Mr. Harry B. Weaver, of this city, who has been untiring in his efforts to prepare a series of accurate and complete photographs.

⁸⁸ In 1804, eleven years after Hunter's death.

NOTES AND NEWS.

Dr. A. D. Atkinson is Physician in Chief to St. Agnes Hospital, Baltimore.

Dr. John Auer is Associate Member, Department of Physiology and Pharmacology, Rockefeller Institute, New York City.

Dr. J. R. B. Branch is Attending Gynecologist to the Macon Hospital, and Anæsthetist to the Williams Private Sanitarium, Macon, Ga.

Dr. Walter V. Brem is Professor of Pathology and Bacteriology in the Los Angeles Department of the College of Medicine of the University of California.

Dr. J. S. Brotherhood is Associate Physician, the Sanitarium, Clifton Springs, N. Y.

Dr. J. I. Butler is President and Manager of the Rodgers Hospital, Tucson, Arizona.

Dr. John W. Churchman is Assistant Professor of Surgery, Yale Medical School, and Assisting Visiting Surgeon, New Haven Hospital.

Dr. A. L. Fisher is Assistant in Orthopedic Surgery, Stanford University, San Francisco, Cal.

Dr. Emil Goetsch is Assistant in Surgery, Harvard Medical School, and Resident Surgeon, Peter Bent Brigham Hospital, Boston, Mass.

Dr. Ernest G. Grey is Assistant Resident Surgeon, Peter Bent Brigham Hospital, Boston, Mass.

Dr. F. Webb Griffith is Surgeon to the Mission, Biltmore and Meriwether Hospitals, Asheville, N. C.

Dr. Louis P. Hamburger, in addition to his appointment in the Johns Hopkins Hospital Dispensary, is Attending Physician to the Union Protestant Infirmary, Hebrew Hospital, Hospital for Women of Maryland, Church Home and Infirmary and Children's Hospital School.

Dr. C. W. Hennington is Surgeon to the Rochester State Hospital, and Surgeon to Outpatient Department of the Rochester General Hospital.

Dr. Arthur D. Hirschfelder is Professor of Pharmacology and Director of the Department of Pharmacology, University of Minnesota Medical School.

Dr. J. Gardner Hopkins is Associate in Bacteriology, Columbia University. Address: 350 Washington Avenue, Brooklyn, N. Y.

Dr. Henry T. Hutchins is Assistant in Gynecology, The Harvard Medical School, Surgeon to the Outpatient Department, The Free Hospital for Women, Brookline, Mass.; Consulting Gynecologist, Rufus S. Frost General Hospital, Chelsea, Mass., and Consulting Gynecologist to the Memorial Hospital, Pawtucket, R. I. Address: 374 Marlborough Street, Boston, Mass.

Dr. Hans Lissner is Assistant in Medicine, the Washington University Medical School, and Resident Pathologist, the Washington University Hospital, St. Louis, Mo.

Dr. David R. Lyman is Clinical Lecturer on Tuberculosis, the Yale Medical School.

Dr. F. W. Lynch is Assistant Professor of Gynecology and Obstetrics, University of Chicago, and Attending Gynecologist and Obstetrician, the Presbyterian Hospital, Chicago, Ill.

Dr. Charles C. Norris is Instructor in Gynecology, University of Pennsylvania, Assistant Gynecologist, Hospital of the University of Pennsylvania, Attending Obstetrician to the Philadelphia Maternity Hospital, and Gynecologist and Obstetrician to the Henry Phipps Institute.

Dr. Francis W. Peabody is Alumni Assistant in Medicine, Harvard Medical School, and Resident Physician, the Peter Bent Brigham Hospital, Boston, Mass.

Dr. Louise Pearce is a member of the staff of the Rockefeller Institute for Medical Research, New York City.

Freiherr Clemens von Pirquet is Professor of Pediatrics, the University of Vienna, Austria; k. k. Obersanitätsrat, and Editor of the "Zeitschrift für die gesamte experimentelle Medizin."

Dr. H. W. Plaggemeyer is Director, the Department of Urological Surgery, Detroit General Hospital, and Visiting Surgeon, Manufacturers' Mutual Hospital, Detroit, Mich.

Dr. R. E. Powell is Demonstrator in Anatomy at McGill University, and Clinical Assistant in Surgery and Genito-Urinary Surgery, the Montreal General Hospital, Canada.

Dr. J. C. Pratt is Assistant in Surgery, the University of California. Address: 291 Geary Street, San Francisco, Calif.

Dr. Alexander Randall is Assistant Instructor in Surgery, University of Pennsylvania, and Assistant Surgeon in the Genito-Urinary Dispensary, University of Pennsylvania.

Dr. S. W. Schaefer is Resident Physician, the Glockour Sanitarium and Hospital, Colorado Springs, Colo.

Dr. Benjamin R. Schenck is Associate Professor of Gynecology, Detroit College of Medicine, Gynecologist to the Harper Hospital, and Consulting Obstetrician to The Woman's Hospital, Detroit, Mich.

Dr. W. G. Sexton is Medical Superintendent of the Hebrew Hospital, Baltimore, Md.

Dr. William Sharpe is Adjunct Professor of Surgery, the New York Polyclinic Hospital; Assistant Surgeon, the New York Neurological Institute, and Attending Neurologist, Hospital for Ruptured and Crippled. Address: 20 West 50th Street, New York City.

Dr. F. J. Sladen is Director, the Department of Medicine, Detroit General Hospital, Detroit, Mich.

Dr. J. M. Slemons is Professor of Obstetrics and Gynecology, the University of California, and Director of the Woman's Clinic, the University of California Hospital. Address: 3404 Clay Street, San Francisco, Calif.

Dr. Joseph T. Smith, Jr., is Instructor in Gynecology, Western Reserve University Medical Department; Assistant Surgeon, Dispensary of Lakeside Hospital, and Western Reserve University Gynecological Department.

Dr. A. de T. Valk is Visiting Physician to the Twin City Hospital, Winston-Salem, N. C., and Lecturer in Anatomy and Physiology to the nurses of that institution.

Dr. A. Raymond Stevens is Instructor in Genito-Urinary Surgery, New York University; Assistant Attending Genito-Urinary Surgeon to Bellevue Hospital, and Chief of the Genito-Urinary Clinic, Presbyterian Hospital Dispensary. Address: 40 E. 41st Street, New York City.

Dr. Solomon Strouse is Associate Attending Physician, the Michael Reese Hospital; Directing Physician, Chicago-Winfield Tuberculosis Sanitarium; Attending Dispensary Physician, Municipal Tuberculosis Sanitarium, and Instructor in Medicine, the University of Illinois. Address: 104 S. Michigan Ave., Chicago, Ill.

Dr. J. H. J. Upham is Professor of Medicine and Clinical Medicine in Sterling, Ohio, Medical College; Attending Physician to St. Francis Hospital, Consulting Physician to Mt. Carmel Hospital, and President of the Ohio State Medical Association. Address: Columbus, O.

Dr. Douglas Vanderhoof is Associate Professor of Clinical Medicine, Medical College of Virginia.

Dr. H. I. Wiel is Assistant in Medicine, Mt. Zion Hospital, San Francisco, Calif.

Dr. Otis B. Wight is Assistant Professor of Gynecology, Medical Department, University of Oregon.

Dr. Helen Watson Winternitz is Lecturer on Anatomy, Johns Hopkins Hospital Training School for Nurses.

Dr. Eleanor B. Wolf is House Physician, New York Infirmary for Women and Children.

Dr. J. M. Wolfsohn is Instructor in Neurology, Leland Stanford Jr. University; Neurologist to the San Francisco Hospital, and Neurologist to the Children's Hospital, San Francisco, Calif.

Dr. P. G. Woolley is Professor of Pathology and Head of the Department of Pathology and Bacteriology, Medical Department, University of Cincinnati, and Director of the Laboratories of the Cincinnati Hospital.

NOTES ON NEW BOOKS.

Practical Physiological Chemistry. By SYDNEY W. COLE, M. A. 7/6. Third Edition. (Cambridge [Eng.]: W. Heffer & Sons, Ltd., 1913.)

This work is intended as an exercise book, largely to aid students to pass examinations in medical chemistry, and it is so arranged as to be useful for students who are not thoroughly grounded in chemistry. Its third appearance would seem to indicate that it has met with a certain success in England, and it may be used by some schools in this country. The author discusses the proteins, carbohydrates and fats, then passes to the chemistry of some foods, the composition of the digestive juices, and the action of certain enzymes. After these introductory chapters he takes up the blood, bile, and urine, and has a final chapter on the detection of substances of physiological interest.

The Psychoneuroses and Their Treatment by Psychotherapy. By PROFESSOR J. DEJERINE AND DR. E. GAUCKLER. Translated by Smith Ely Jelliffe, M. D. \$4.00 (Philadelphia and London: J. B. Lippincott Company, 1913.)

At a moment when so much attention is paid to mental disorders, it is all important to have all the aid to be obtained from every source, and it is especially valuable to secure the opinions of foreigners whose work along these lines has been more thorough and exhaustive than ours up to the present. So few of our physicians read French easily that they may consider themselves very fortunate to have secured this admirable translation of an important work. Dejerine's practice and writings have been of the utmost interest to all psychiatrists, for he has worked out his

own therapy with originality and has been a leader in the modern treatment of psychoneuroses. His book is divided into three parts; the first analytical, or "the study of all the symptoms which are observed in the course of the psychoneuroses"; the second synthetic, or the explanation of "the general mechanism of the foundation of the psychoneuroses, as well as their variations and nature"; the third therapeutic, which needs no definition. This is a book well worth study by the general practitioner.

Irritability. By MAX VERWORN, M. D. (New Haven: Yale University Press. London: Henry Frowde, 1913.)

Dr. Verworn, Professor at the University of Bern, was invited to deliver the Silliman Lectures at Yale University in 1911, and this volume is the result. The author's reputation as a brilliant physiologist has been long established, and his work is, therefore, of very great interest as presenting for the first time in English a comprehensive treatise of irritability or the "effect of stimuli on living substance." To the advanced student of physiology it will be a great aid, and stimulus to new investigations along fresh lines for Dr. Verworn is most suggestive and his book is full of meat.

An Elementary Study of the Brain. By EBEN W. FISKE, M. D. Illustrated. \$1.25. (New York: The Macmillan Company, 1913.)

For certain college and possibly high-school courses this is an excellent work, from which students will get a very clear idea of the structure of the brain. It is based on the dissection of the brain of the sheep, and should prove useful just as books detailing

the anatomy of the cat, frog, and lobster are used for demonstration courses in biology or zoology. With this book an energetic, bright student, working alone, could acquire much information during a summer holiday, and thus prepare himself for more advanced work in the anatomy of the human brain.

Les Épanchements du Péricarde. Par DOCTEUR GERMAIN BLECHMANN. (Paris: J. B. Baillière et Fils, 1913.)

As is common with French theses, the author dedicates his work to many of his professors and others, amongst whom it is pleasant to note the name of Thomas Morgan Rotch; and in the text he refers frequently to Rotch's early experimental work on pericarditis. The thesis is a careful study of this disease; the author believes that the subxyphoid puncture is the best means of diagnosing a pericardial effusion, and that, along with surgical measures that may be necessary there is room for a new active medical treatment which is being developed. This treatment, as the author states, will justify Wright's so frequently repeated remark that "the physician of the future will be an immunisator." A valuable bibliography accompanies the work, which is of special interest to the internist.

Sterility in the Male and Female and its Treatment. By MAX HÜHNER, M. D. \$2.00. (New York: Rebman Company, 1913.)

Dr. Hühner's findings are based upon experimental work of a nature unpleasant to undertake, and he deserves credit for his investigations, which, presented with greater modesty, would make a better impression. One-half this fair-sized volume of 250 pages gives the author's views, as based largely on his own work, the other half is merely a record of his case histories. The whole might have been condensed with profit into less than one-half and the results offered in a more concise and practical manner. That the author has added something to our knowledge of this trouble is unquestionable, and so the book has its value, but its value hardly calls for book form. As a journal article it would have had many readers and found its true place.

Massage: Its Principles and Technic. By MAX BOHM, M. D., Edited, with an introduction, by CHARLES F. PAINTER, M. D. Illustrated. \$1.75. (Philadelphia and London: W. B. Saunders Company, 1913.)

The illustrations of this book, with the simple accompanying text, make it an exceptionally useful one for both students and nurses. The general principles of massage are well described, and the size of the volume makes it acceptable. It does not pretend to cover very special forms of massage, as of the eye, the larynx, female generative organs, etc., but is limited to the massage of the leg, arm, back, abdomen, etc., such as is usually required of nurses and masseurs.

Sex: Its Origin and Determination. By THOMAS E. REED, M. D. (New York: Rebman Company.)

The author has prepared an interesting work to substantiate his theory that the origin and determination of sex, the course of acute disease, parturition, etc., are the result of the metabolic (anabolic and katabolic) cycle in man, but the proof he brings to bear is inconclusive. How far the human system and its many functions, both normal and abnormal are dependent on daily, weekly, or monthly cycles, is a much mooted question. Dr. Reed has brought together much material to demonstrate the effect of these cycles, but a good deal of the evidence is hypothetical, and the origin of sex still remains a problem to be worked out by experiment rather than by theorizing on such an uncertain factor as the lunar or tidal influence on the earliest forms of life.

Collected Papers by the Staff of St. Mary's Hospital (Mayo Clinic) for 1912. Illustrated. \$5.50. (Philadelphia and London: W. B. Saunders Company, 1913.)

This is a fresh volume of very interesting papers from the Mayo Clinic. They have appeared before in various journals, but, gathered together in this handsome form, they furnish an excellent index of the broad scope and high quality of the work done by the Mayo brothers and their staff.

Summaries of Laws Relating to the Commitment and Care of the Insane in the United States. Prepared by JOHN KOREN. \$1.00. Published by The National Committee for Mental Hygiene. (New York, 1913.)

The National Committee, in publishing this volume has done an excellent piece of work. The compilation of these laws is important for the physicians, lawyers, and social service workers, especially when our state legislatures are preparing to pass new or modify old laws in regard to the insane. As our views in caring for this class are undergoing radical changes, it is likely that the existing laws will be much changed within a few years, and, therefore, this volume will be of very great help to those intrusted with the preparation of new laws.

Burdett's Hospitals and Charities, 1913. Being the Year Book of Philanthropy and the Hospital Annual, containing an exhaustive record of hospital work for the year. By SIR HENRY BURDETT, K. C. B., K. C. V. O. (London: The Scientific Press Limited, 28 and 29 Southampton Street, Strand, W. C.)

This standard annual is now in the 24th year of publication. It seems surprising that, dealing as it does with the statistics of many thousand institutions, it should find it practicable to publish them fully at such an early date in the current year. The editor renews his plea for the establishment of an institution year by each hospital, to correspond with the calendar year, so that all statistics may be comparable for an identical period of time.

It is gratifying to read his expression of a willingness to furnish necessary information by letter to hospital officials who may desire instruction or advice in the line of hospital management or even of construction.

The book is of peculiar interest to Englishmen in English hospitals, because it treats largely of local conditions, such as "King Edward's Fund," the "League of Mercy," "Hospital Saturday and Sunday," and hospital conditions arising in consequence of the new compulsory insurance for workmen. These details, however, furnish valuable hints for the betterment of conditions throughout the world and teach lessons of general application.

Apropos of medical education, it is gratifying to see the Hospital Annual advocating grants from the government in aid of voluntary hospitals connected with medical teaching in recognition of the value of their educational work. Would that similar pecuniary recognition could come in the United States to those hospitals who are doing good service in the proper education of physicians and nurses. The book is full of material for thought and should be in the hands of every hospital superintendent.

Diseases of the Heart and Aorta. By ARTHUR D. HIRSCHFELDER, M. D. Second Edition. \$6.00. (Philadelphia and London: J. B. Lippincott Company.)

It is a pleasure to announce the appearance of a second edition of this valuable work. Full discussions, with a valuable bibliography of the electrocardiograph, of the cardiac irregularities, of the rôle of carbon dioxide in heart disease, of syphilitic disease of the aorta, and of chronic hypertension, has brought the new edition abreast of the many new developments in the realm of cardiovascular pathology and make it the most useful of all English text-

books dealing with this field. As in the first edition, the numerous illustrations greatly assist one in obtaining a proper comprehension of the subject matter.

George Crocker Special Research Fund. Vol. IV. Studies in Cancer and Allied Subjects. (New York: Columbia University Press, 1913.)

The eight papers in this handsomely printed, and finely illustrated volume all deal with the anatomy and development of the salivary glands in the mammalia. Carmalt, Huntington, and Schulte are the three contributors, the work of the two latter amplifying observations already begun and reported upon by Carmalt, who died in 1905, after having made interesting investigations of the problem noted. The salivary glands were studied in the hope of throwing light "on the phylogenetic aspect of the epithelial neoplasms of this area." The volume is an important addition to our knowledge of these glands.

Acute Poliomyelitis (Heine-Medin's Disease). By DR. IVAN WICKMAN. Translated by DR. F. WM. J. A. M. MALONEY. \$3.00. (New York: The Journal of Nervous and Mental Disease Publishing Company, 1913.)

This is an important contribution to the literature of the disease which, within the last few years, has been so profoundly studied with such brilliant results in America. To students at Harvard belongs the honor of having found the transmitting agent in the fly, and to Drs. Flexner and Noguchi of the Rockefeller Institute the glory of having isolated the causative organism. The monograph by Dr. Wickman gives an excellent picture of the disease, and it is fortunate that the editors of the Nervous and Mental Disease Monograph Series selected it for translation.

Pathological Inebriety: Its Causation and Treatment. By J. W. NATLEY COOPER. \$1.50. (New York: Paul B. Hoeber, 1913.)

Physicians who undertake the scientific care of inebriates will find this small brochure of value. Dr. Cooper has had a large experience with this class of patients, and what he says in regard to their treatment is well worth careful reading and consideration. Chronic or periodic drinkers are extremely difficult to treat so as to effect a radical cure and prevent their returning to their old habits, and, therefore, any serious work of this nature is useful.

Vaccine and Serum Therapy. By EDWIN HENRY SCHORER, M. D. Second Revised Edition. \$3.00. (St. Louis: C. V. Mosby Company, 1913.)

In the last four years, since this book first appeared in 1909, vaccines and serum therapy have been much studied and we have a better comprehension of their value than at that time. Dr. Schorer has incorporated the newer findings in his second edition and otherwise added to his work, which can be recommended to the profession as a thorough and clear presentation of the subject.

A Reference Handbook of The Medical Sciences. Third Edition. Edited by THOMAS LATHROP STEDMAN, M. D. Vol. II. BADCHL. (New York: William Wood & Co., 1913.)

The three longest articles in this volume, as might almost be guessed, are on the brain, 165 pages; the blood, 125; and the breast, 55. These are well prepared, and, in view of their importance in medicine, not too long. Cancer is dealt with in 15 pages, which seems short. But this merely draws attention to one of the obvious difficulties in the preparation of such a handbook. Different contributors cannot be expected to treat their subjects in similar manner, for one will write profusely, the other briefly and compactly. The original handbook was highly appreciated by the profession in its

day, and there is no doubt that Dr. Stedman's will prove even more complete and valuable when finished. The two volumes just issued promise excellently for the success of the entire eight. Anyone who undertakes such a work deserves the hearty thanks of all its readers, and it is certain that the profession-at-large will warmly endorse this new edition.

Indigestion, Constipation and Liver Disorder. By G. SHERMAN BIGG, F. R. C. S. (Edinburgh). \$1.50. (Hoeber: New York, 1913.)

This is a book of slight value and an unpleasant impression is aroused in looking through it to find that remedies are quoted with the makers' names or initials, *e. g.*, P. D. & Co.; B. W. & Co.; Fairchild; Mellin; Messrs Kirby of Newman St.; Van Horn and Sautell, etc.; as though the author were writing to advertise the products of various firms.

Blood-Pressure, from the Clinical Standpoint. By FRANCIS ASHLEY FAUGHT, M. D. Illustrated. \$3.00. (Philadelphia and London: W. B. Saunders Company, 1913.)

The author speaks of this book as a "little work," but it covers 270 fair sized pages. As there is no other comprehensive book on blood-pressure in English this one will serve the student well; in it he will find most of the needed information to guide him along his way. Printed on thick paper it is heavier than necessary for which the publishers are to blame.

Blood Pressure in General Practice. By PERCIVAL NICHOLSON, M. D. \$1.50. (Philadelphia and London: J. B. Lippincott Company, 1913.)

"This treatise therefore starts with the assumption that the writer is dealing with a new subject, and an effort has been made to present the material given in as simple a manner as possible." The manner has been carried out too simply, with the result that the book in places is not clear, and as an entity has small value.

Diagnostic Methods: Chemical, Bacteriological, and Microscopical. By RALPH W. WEBSTER, M. D. Third Edition, Revised and Enlarged. Illustrated. (Philadelphia: P. Blakiston's Son & Co., 1913.)

Three editions within four years speaks well for the popularity of this work, and it deserves this mark of success. The author keeps his book up-to-date, and has covered the ground thoroughly, so that the work is a serviceable one for students and general practitioners.

Manual of Operative Surgery. By JOHN FAIRBAIRN BINNIE, C. M. (Aberdeen), etc. Sixth Edition, Revised and Enlarged. Illustrated. \$7. (Philadelphia: P. Blakiston's Son & Co., 1913.)

This surgery well merits its popularity and to each edition the author adds something to bring the work up-to-date and thus make it really serviceable for the advanced surgeon. Rare and difficult operations are described in detail, because any man, who rightly calls himself a surgeon, should know how to perform the simpler operations when he commences practice. It is an excellent book, clearly written by a man of wide experience and sound judgment.

A Manual of Venereal Diseases. By SIR ALFRED KEOGH, K. C. B., and others. Second Edition. Revised and largely Rewritten. \$3.75. (London: Henry Frowde and Hodder & Stoughton, 1913.)

This work is essentially a treatise on syphilis, as out of 280 pages, 230 are devoted to this disease. Discussion of gonorrhœa, soft-chancres and balanitis takes up the remaining pages. Im-

portant as syphilis is, yet treated only as a venereal disease, the disproportion of space allotted to it and gonorrhœa seems a mistake, since the latter trouble, from several points of view, is as far reaching in its disastrous results as the former. It is, leaving this point out of consideration, a useful book for the general practitioner, and we are glad to note its second appearance.

Malaria. By GRAHAM C. HENSON, M. D. Illustrated. \$2.50. (St. Louis: C. V. Mosby Company, 1913.)

Dr. Bass in a brief introduction warmly indorses this work, and his endorsement is merited. Dr. Henson has written an excellent manual on the etiology, pathology, diagnosis, prophylaxis, and treatment of this disease, and physicians throughout the South will find it most useful. It is a good practical handbook, covering all the essential features of malaria, which, unfortunately, is not yet generally recognized as one of our worst diseases, and in parts of the country most prevalent. It is to be hoped that Dr. Henson's treatise will help to awaken the public to the urgent need of action in eradicating malaria wherever it exists, and this is generally not a difficult or very costly task.

A Manual of Surgery. By FRANCIS T. STEWART, M. D. Third Edition. Illustrated. \$4. (Philadelphia: P. Blakiston's Son & Co., 1913.)

This is one of the many surgical manuals, which are on the market, and which have found favor with the profession. Students of surgery will be glad to have the revised edition of Dr. Stewart's work which contains important additions and is a prac-

tical book. As it covers a great deal of ground, the author does not go into minute detail as to operations, but the general outlines are clearly presented.

Vicious Circles in Disease. By JAMIESON B. HURRY, M. D. (Cantab.). Illustrated. Second and Enlarged Edition. \$3. (Philadelphia: P. Blakiston's Son & Co., 1913.)

This work can be read with benefit by the general practitioner, for unless his experience is large he frequently fails to recognize the existence and number of these vicious circles, which are found associated with almost all organs and systems. The make-up of the book is more like that of a gift-book, than a serious medical work—pages gilded on their edges, and unusual type might cause the reader to question the value of the work as he picks it up, and to put it aside as unimportant. It is unfortunate that it should appear in this somewhat fantastic dress, for it merits attention.

Progressive Medicine. Edited by HOBART AMORY HARE, M. D., etc. Assisted by LEIGHTON F. APPLEMAN, M. D., etc. Vol. III. September, 1913. (Philadelphia and New York: Lea & Febiger.)

Ewart of London, Gottheil of New York, with Davis and Spiller of Philadelphia respectively review the diseases of the thorax and its viscera, dermatology and syphilis, obstetrics, and diseases of the nervous system. The reviews are satisfactory and aid the busy doctor to keep himself abreast of the best thought and practice both here and abroad.

BOOKS RECEIVED.

Book on the Physician Himself and Things that Concern His Reputation and Success. By D. W. Cathell, M. D. The twelfth and final edition, enriched and strengthened by the author and his son, William T. Cathell, A. M., M. D. 1913. 8vo. 407 pages. F. A. Davis Company, Philadelphia.

Pathological Inebriety: Its Causation and Treatment. By J. W. Astley Cooper. With Introduction by Sir David Ferrier, M. D., F. R. S. 1913. 12°. 151 pages. Paul H. Hoeber, New York.

The Narcotic Drug Diseases and Allied Ailments. Pathology, Pathogenesis, and Treatment. By Geo. E. Pettey, M. D. Illustrated. 1913. 8°. 516 pages. F. A. Davis Company, Philadelphia.

Golden Rules of Diagnosis and Treatment of Diseases. Aphorisms, Observations, and Precepts on the Method of Examination and Diagnosis of Diseases, with Practical Rules for Proper Remedial Procedure. By Henry A. Cables, B. S., M. D. Second edition, revised and rewritten. 1913. 12°. 318 pages. C. V. Mosby Company, St. Louis.

Surgery of the Eye. By Ervin Török, M. D., and Gerald H. Grout, M. D. With 509 original illustrations, 101 in colors, and 2 colored plates. 1913. 8°. 507 pages. Lea & Febiger, Philadelphia and New York.

Clinical Pathology. By P. N. Panton, M. A., M. B., B. C., Cantab. With 13 plates (11 colored) and 45 illustrations in the text. 1913. 8vo. 446 pages. P. Blakiston's Son & Co., Philadelphia.

The Difficulties and Emergencies of Obstetric Practice. By Comyns Berkeley, M. A., M. D., B. C., Cantab., F. R. C. P., Lond., M. R. C. S., Eng., and Victor Bonney, M. S., M. D., B. Sc., Lond., F. R. C. S., Eng., M. R. C. P., Lond. With 287 illustrations. 1913. 8°. 787 pages. P. Blakiston's Son & Co., Philadelphia.

Text-Book of General Pathology. Edited by M. S. Pembrey and J. Ritchie. 1913. 8°. 773 pages. Longmans, Green & Co, New York; Edward Arnold, London.

Vaccine and Serum Therapy. Including also a Study of Infections, Theories of Immunity, Specific Diagnosis and Chemotherapy. By Edwin Henry Schorer, B. S., M. D., Dr. P. H. Second revised edition. 1913. 8°. 300 pages. C. V. Mosby Company, St. Louis.

Nervous and Mental Disease Monograph Series No. 16. Acute Poliomyelitis (Heine-Medin's Disease). By Dr. Ivan Wickman. Authorized English Translation by Dr. J. Wm. J. A. M. Maloney, F. R. S. Ed. Illustrated. 1913. 8°. 135 pages. The Journal of Nervous and Mental Disease Publishing Company, New York.

The Report of the Philadelphia Baby Saving Show and the Proceedings of the Conference on Infant Hygiene. Edited by the Publication Committee. Illustrated. 1913. 8°. 270 pages. Published by the Executive Committee.

General Index. Transactions of the Illinois State Medical Society, 1850-1898. Edited by Carl E. Black, A. M., M. D. 1913. 4°. 81 pages. Published under the Direction of the Illinois State Medical Society, Springfield.

Preventive Medicine and Hygiene. By Milton J. Rosenau. With chapters upon Sewage and Garbage, by George C. Whipple; Vital Statistics, by Cressy L. Wilbur: The Prevention of Mental Diseases, by Thomas W. Salmon. 1913. 8°. 1074 pages. D. Appleton & Co., New York and London.

Summaries of Laws Relating to the Commitment and Care of the Insane in the United States. Prepared by John Koren for the National Committee for Mental Hygiene. 1912. 8°. 297 pages. The National Committee for Mental Hygiene, New York.

- Diseases of the Ear.* By Philip D. Kerrison, M. D. 331 illustrations in text and 2 full pages in color. [1913.] 8°. 588 pages. J. B. Lippincott Company, Philadelphia and London.
- Ophthalmoscopic Diagnosis.* Based on Typical Pictures of the Fundus of the Eye, with Special Reference to the Needs of General Practitioners and Students. By Dr. C. Adam. Translated by Matthias Lanckton Foster, M. D. With 86 colored pictures on 48 plates and 18 illustrations in the text. [1913.] 4°. 229 pages. Rebman Company, New York.
- A Course in Normal Histology.* A Guide for Practical Instruction in Histology and Microscopic Anatomy. By Rudolph Krause. Translation from the German by Philipp J. R. Schmahl, M. D. With 30 illustrations in text and 208 colored pictures, arranged on 98 plates after the original drawings by the author. [1913.] 4°. Part I, 86 pages. Part II, 406 pages. Rebman Company, New York.
- Therapeutics of the Gastro-Intestinal Tract.* By Dr. Carl Wegele. Adapted and Edited, with Additions on the Diagnosis of the Diseases of the Esophagus [etc.]. By Maurice H. Gross, M. D., and I. W. Held, M. D. With 52 illustrations in the text and 2 figures in colors on one plate. 1913. 8°. 329 pages. Rebman Company, New York.
- Sterility in the Male and Female and Its Treatment.* By Max Hühner, M. D. 1913. 8°. 262 pages. Rebman Company, New York.
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- Diseases of the Stomach.* Including Dietetic and Medicinal Treatment. By George Roe Lockwood, M. D. Illustrated with 126 engravings and 15 plates. 1913. 8°. 624 pages. Lea & Febiger, Philadelphia and New York.
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- General Malaria Committee.* Proceedings of the Third Meeting held at Madras, November 18, 19 and 20, 1912. Fol. 289 pages. 1913. Government Central Branch Press, Simla.
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- Oxford Medical Publications.* Publishers: Henry Frowde, London; Hodder & Stoughton, London. The following 5 volumes.
- A Manual of Venereal Diseases.* Introduction by Sir Alfred Keogh, K. C. B. History, Statistics, Invaliding, etc., Brevet Colonel C. H. Melville, R. A. M. C. Clinical Pathology and Bacteriology, Brevet Colonel Sir William Leishman, K. H. P., F. R. S., R. A. M. C. Clinical Course and Treatment, Major C. E. Pollock, R. A. M. C. Second edition revised and largely re-written. With new matter by Major L. W. Harrison, R. A. M. C. 1913. 8°. 318 pages.
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- A Manual of Surgery.* By Francis J. Stewart, M. D. Third edition. With 571 illustrations. 1913. 8°. 742 pages. P. Blakiston's Son & Co., Philadelphia.
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- Stellar Motions.* With Special Reference to Motions Determined by Means of the Spectrograph. By William Wallace Campbell, Sc. D., LL. D. 1913. 8°. 328 pages. Yale University Press, New Haven; Henry Frowde, London.
- Saint Thomas's Hospital Reports. New Series.* Edited by Dr. J. J. Perkins and Mr. C. A. Ballance. Vol. XL. 1913. 8°. 217 pages. J. & A. Churchill, London.
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- Studies Concerning Glycosuria and Diabetes.* By Frederick M. Allen, A. B., M. D. 1913. 8°. 1179 pages. W. M. Leonard, Boston.
- Surgery of the Vascular System.* By Bertram M. Bernheim, A. B., M. D. With 53 illustrations in text. [1913.] 8°. 104 pages. J. B. Lippincott Company, Philadelphia and London.
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- The Diseases of Children.* By Henry Enos Tuley, M. D. With one hundred and six engravings and three colored plates. Second revised edition. 1913. 8°. 684 pages. C. V. Mosby Company, St. Louis.

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- Studies in Cancer and Allied Subjects. The Study of Experimental Cancer. A Review.* By William H. Woglom, M. D. Conducted under the George Crocker Special Research Fund at Columbia University. Vols. I, III, and IV. 1913. Fol. 288 pages. Columbia University Press, New York.
- A Treatise on the Diseases of Women.* By Palmer Findley, B. S., M. D. Illustrated with 632 engravings in the text and 38 plates in colors and monochrome. 1913. 8°. 954 pages. Lea & Febiger, Philadelphia and New York.
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- Diagnosis of the Malignant Tumors of the Abdominal Viscera.* By Professor Rudolph Schmidt. Authorized English version by Joseph Burke, Sc. D., M. D. [1913.] 4°. 361 pages. Rebman Company, New York.
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INTESTINAL OBSTRUCTION: FORMATION AND ABSORPTION OF TOXIN.

By DAVID M. DAVIS, M. D.,
Assistant in Pathology.

(From the Hunterian Laboratory of Experimental Pathology, The Johns Hopkins University.)

The historical side of the investigation of intestinal obstruction has been gone over so frequently and well by the recent writers that only a very brief outline will be given here.

Three principal theories have been propounded to explain the death which occurs when the gut is obstructed: 1, that of a nervous reflex; 2, that of infection; 3, that of intoxication. The first of these has received little attention of late. The second has had strong support from such investigators as Borszecky and Genersich (12) and lately Murphy and Vincent (49). Their case is, however, at best doubtful, and an overwhelming amount of evidence has been brought forward by Albeck (1), Kukula (41), Clairmont and Ranzi (16), Roger and his associates (60-64), McClure (44), Whipple, Stone and Bernheim (67, 68, 69), etc., to show that a strong toxic factor is at work in these cases and that death may occur without any infection of the peritoneum or blood. Other theories at variance with the principal ones are those of Braun and Boruttau (13), who considered that the symptoms in ileus were due to a cerebral anemia consequent upon splanchnic congestion and dehydration of the blood; and of Hartwell, Hoguet and Benedict (28-29), who felt that no toxic element was present, but that dehydration of the organism was the cause of the harm. Whipple, Stone and Bernheim (70), by immunizing dogs with sublethal doses of the toxic contents of closed duodenal loops, made it possible for them to remain alive with closed duodenal loops over a length of time entirely

unknown with unimmunized animals. These experiments leave no doubt that a toxin found in the intestinal contents is responsible for a great part, at least, of the symptoms occurring in uncomplicated ileus.

The point about which discussion still goes on is that of the origin of this toxin. The first writers on the subject—Amussat (4), Humbert (36), Bouchard (11), Albu (?), Nikolaysen (51), etc., conceived that putrefaction of the intestinal contents gave rise to the noxious substances. This view was upheld by the experiments of v. Albeck (1), Kukula (41), Clairmont and Ranzi (16), McClure (44), and many others. Roger, however, after numerous experiments (60-64), came to the conclusion that normal bowel contents were toxic enough to account for the symptoms. He thought first of decomposed food, and later of the intestinal secretions, toward the latter of which he inclined when he found an extract of intestinal wall quite toxic. Draper-Maury (22-23) supported this view after a multitude of experiments. The writer has found normal intestinal contents of dogs containing the ordinary food residues fatally toxic when given intravenously to other dogs. Matthews (46) advanced the idea that excision of the duodenum was incompatible with life, owing probably to the absence of some internal secretion. His theory has received no support, however, since his findings do not agree with those of other experimenters.

CLOSED LOOPS.

In dealing with the intestinal contents in ileus, it has been found of advantage to make two obstructions, thus confining the material between them, and making the entrance of food, or the withdrawal of any of the contents, as, for instance, by vomiting, impossible. The material which is found in these loops is the resultant of a number of processes going on simultaneously, and no one of them must be forgotten when the whole is considered. These processes are:

- Secretion of digestive fluids;
- Breaking up of food by digestive ferments;
- Putrefaction of contents by bacteria;
- Absorption of substances by the mucosa;
- Excretion of waste products by the mucosa.

The last-named factor is one concerning which our knowledge is unsatisfactory, in spite of the large amount of careful work done upon it. The pioneers in the field were Bischoff and Voit (10), who were followed by Muller (48), Rieder (59), v. Moraczewsky (47), Hermann (31), Ehrenthal and Blitzstein (25), Fr. Voit (66), Berenstein (9), Klecki (38-39), Corlette (20), and many others. It was found that starving animals still continued to form a certain amount of dark, pasty feces for an indefinite period, and soon the aid of the closed intestinal loop, first made by Halsted (26), was also invoked toward the elucidation of the problem. It showed that a very considerable amount of material was the result of the mucosal activity, but what proportion was necessary digestive secretion, and what proportion waste matter, still remains unknown. At any rate, there are many arguments in favor of the idea that the intestinal mucosa regularly has an important excretory function. The possibility immediately arises of this excrementitious matter providing some or all of the toxic substances.

As has been stated above, the products of putrefaction were first seized upon as the most likely to be toxic. Efforts to isolate toxic split products, for example, those of Kukula, Barger and Nesbitt (6, 7, 41, 50), have been unsatisfactory. The possibility of decomposed food as a source was ruled out by the use of the closed loop, from which food is excluded. When the mucosa was destroyed in a closed loop by Whipple (68), the clinical course was not at all characteristic; the animal died of septicaemia, and the loop contents were not toxic. This indicates that the mucosa is necessary for the development of the ordinary toxin. The efforts to fix the blame on bacteria being on the whole unsuccessful, it occurred to the writer to try to test the toxicity of the intestinal secretion, while still uninfluenced by microorganisms.

DRAINED DUODENAL LOOP.

The first steps towards this end were taken in the observation of intestinal loops, which, instead of being closed, were drained to the outside. The ends of the loop were fastened to the skin, and rubber tubes put in them. It was difficult to keep the tubes in place, but even after they had come out, the loop was easily washed by inserting a catheter. Whipple (69) has performed this experiment frequently on dogs, and often they die with typical symptoms of ileus in spite of the drain-

age. The writer prepared one cat in this manner. It remained strong and healthy during the time (10 days) when daily lavage was done. The washings showed a slight yellowish brown coloration, and contained flakes of mucus. Corlette (20) shows that this coloration is due to a pigment secreted by the mucosa, and not to blood pigment. The total amount, mixed, of course, with wash water, for the ten days was about 1200 cc. It was preserved with chloroform and toluol. This was evaporated at 60° C. to a volume of 115 cc., filtered, and injected into the veins of a dog weighing 8 lbs. The dog died in 4½ hours, with the symptoms and autopsy findings described as typical for closed loop fluid by Whipple.

FISTULA EXPERIMENTS.

It was desired, however, to devise an experiment which would do away altogether with obstruction, and allow the mucosa to secrete as nearly as possible under normal conditions. To this end dogs were prepared by tying off the bile duct, dissecting the pancreas away from the duodenum or removing it altogether, and opening a fistula 30-35 cm. below the pylorus. Three dogs were operated upon thus, the details being given in the appended protocols. The intestinal secretion failed to flow out freely, so that lavage was again necessary. The whole procedure was completed, however, in a short time—much less than that required for the death of animals from closed duodenal loops—and at the end there was no perceptible lesion of the mucosa except a slight hyperaemia from handling, opposite the head of the pancreas. The fluid obtained in this manner when given intravenously to dogs had, in all cases, effects identical with those caused by closed loop fluid.

DISCUSSION.

In this series of experiments, the material dealt with was washed out of the intestine within a few minutes at most after its secretion and preserved at once with chloroform and toluol. This effectually removes the possibility of bacterial action in the formation of a toxic substance. Nothing is present except that which has been produced by the intestine itself. It may indeed be argued that the intestine is in a pathological condition from the operation. This possibility cannot be denied, yet the handling of the gut was not greater than that suffered by it in great numbers of operations performed daily on men and animals, in which no noteworthy toxic symptoms are seen. At any rate it seems clear that the intestinal mucosa is capable, under certain conditions at least, of producing unaided some very toxic substance or substances.

ABSORPTION FROM THE INTESTINE.

The next question that arose was of the manner in which these or other toxic substances gained entrance to the blood stream. It is evident from the work of almost every investigator that in animals and men a fatal toxæmia may exist without demonstrable lesions of the mucosa. Must it be assumed that the normal mucosa can absorb the toxin? Upon consulting the numerous researches (8, 17, 19, 30, 32, 35, 52, 58, etc.) made by physiologists on the absorption taking place in the small intestine, one sees that a conception of the normal mucosa is a very difficult one. It acts in many ways as a semi-

permeable membrane, obeying the laws of osmosis and diffusion, yet very slight influences serve to upset it, and cause it to absorb substances in a way very different from the normal. For instance, the sugar in a 2 per cent solution of dextrose will be absorbed at a very different rate when the carbohydrate is placed in a 5 per cent solution of NaCl from that at which it is absorbed when placed in a .9 per cent solution of NaCl. Again, the one-sided permeability of the mucosa to NaCl has been regarded as a criterion of its normal state; but Cohnheim (17, 18, 19) has shown that the mucosa may suffer some damage yet still retain this one-sided permeability. If mechanical factors can cause the mucosa to absorb toxins, one would expect every operation on the bowel to be followed by a toxæmia. In obstructions and closed loops, however, there are other factors; first, an accumulation of toxic products in the often distended intestine, with a possible concentration due to absorption of water from the mass. It is known (52-58) that water under all conditions is absorbed from the intestine much more rapidly than organic solids, presumably consisting of very large molecules. Secondly, the substances concentrated or dilute in this mass might, since the epithelium is so sensitive, act as mucosal poisons, breaking down a normal impermeability of the intestine to such toxic substances. To test these points, two series of experiments were carried out, one, absorption experiments with toxin, the other, absorption experiments with phenolsulphonephthalein. The experiments with toxin will be described first.

ABSORPTION OF TOXIN.

Fresh duodenal loops were made in dogs, and into them were introduced at the time of operation fluids of known toxicity from other closed loops, which had been allowed to go on 3-4 days. One exception to this rule was in experiment 7, where fresh, unpreserved loop contents of unknown toxicity from a dog just dead, were used. It was to be expected that if the normal mucosa was capable of absorbing this toxin, or if the contents themselves would influence the mucosa, chemically or otherwise, to absorb the toxin, that the animals would begin very soon to show toxic symptoms. They did not do so, however, the clinical course in these cases being exactly the same, in symptoms and length of time, as that of dogs with closed loops not treated in any way at the time of operation. Evidently the supplied toxin remained entirely harmless in the loop during the first 24 hours, at least.

ABSORPTION OF PHENOLPHTHALEIN.

If the toxic symptoms depend upon the absorption by an injured mucosa of the poison (Albeck (1), Murphy and Vincent (49), Hartwell and Hoguet (28)), the absorption of an easily recognizable dye, like phenolsulphonephthalein from the intestinal lumen, might be of interest. Since Rowntree and Geraghty have shown (65) that 60-80 per cent of this dye is excreted within an hour by the kidneys of healthy animals, the quantity appearing in the urine will give an excellent indication of the proportional amounts absorbed by the mucosa. It must be understood that the absorption of a comparatively simple substance like phenolsulphonephthalein by the intestinal mucosa will not necessarily be parallel at all to the

absorption of complex organic compounds, such as we conceive this ileus toxin to be.

The technique of the experiment was to inject into the closed loops with a fine hypodermic needle 1 cc. of a solution of phthalein, containing 6 mg. of the dye. The urine was then withdrawn by catheterization at the end of 2, 4, 6 and about 24 hours after the injection, the bladder being washed out with warm water each time. The percentage of dye was determined by means of a du Bose colorimeter. Female cats were utilized as a rule. The excretion of the first six hours was considered as most significant. Other experiments were also made in which the dye was given per os, or injected directly into the normal intestine. The following table gives the results:

CHART A.
PHENOLSULPHONEPHTHALEIN EXCRETION.

No.	Dye given	Time of injection	Per cent of dye excreted in urine						Remarks
			2 hrs.	4 hrs.	6 hrs.	Total 6 hrs.	24 hrs.	Total 24 hrs.	
46	Into closed low ileum loop, cat.	At time of operation.	0.6	0.9	1.30	2.8	28.5	31.3	
50do.....do.....		0.7	11.2	21.9	6.0	7.9	
61do.....do.....	14.8	2.85	217.6	Loop gangrenous; circulation interfered with?
58	Into closed low ileum loop, dog.do.....	1.06	4.0	2.2	7.28	
48	Into closed duodenal loop, cat.do.....		8.0	20.0	28.0	14.0	42.0	
54do.....do.....	1.95	5.1	4.0	11.05	15.8	26.9	
63do.....do.....	2.3	2.3	2.1	6.7	
70do.....	24 hrs. after operation.	50.0	12.0	62.0	Injection must have gone subcutaneously, not into loop. Much distended.
		48 hrs. after operation.	Trace	2.5	2.2	
75do.....	24 hrs. after operation.	2.41	1.1	0.4	4.0	
		48 hrs. after operation.	4.0	Trace	4.0	
79do.....	48 hrs. after operation.	7.0	7.0	
56	Into closed duodenal loop, dog.	At time of operation.	0.92	8.32	6.25	15.5	
124	Into normal duodenum, dog.do.....	16.6	1.90	11.1	46.7	22.0	68.9	
	By stomach tube.do.....	6.6	4.0	1.6	12.2	
do.....do.....	1.4	4.17	6.6	12.2	
do.....do.....	2.45	7.0	9.45	
125	By stomach tube, dog.do.....	2.03	1.6	3.7	
127	Per os, humando.....	6.25	Trace	7.0	
do.....do.....	1.6	3.0	2.1	6.8	
128	Into duodenum, dog.do.....	10.9	9.8	3.77	24.5	

1 7½ hours. 2 Approximately.

Average of closed low ileum loops in 6 hrs., 7.39%.
Average of closed duodenal loops in 6 hrs., 15.31%.
(Averages include only injections made at time of operation.)
Average of injections in normal duodenum, 35.6%.
Average of administrations by stomach tube, dog, 9.38%.

Difficulty was encountered in introducing the dye into the loops on the days following the operation. The few observations made seem to indicate that absorption of phthalein is unusually low in these late loops. This is in accord with the experiments of physiologists made with many other substances. It gives no support to the contention that injury to the mucosa increases its absorptive powers. The table points rather consistently toward a more rapid absorption in the upper part of the small intestine than in the lower part. Aside from this, the results are subject to a very serious error, in that absorption varies with the concentration, and it is impossible to control the concentration of the dye in the intestine. Even in the loops, the quantity of fluid present is very inconstant. This fact also undoubtedly accounts for the low absorption when the phthalein is given by mouth.

DISCUSSION.

What conclusion, then, is to be drawn from these several considerations? If we grant that toxic substances are present in the normal intestine, we can go far on that hypothesis. It has been seen that the normal duodenal mucosa is apparently impermeable to the toxin; in addition the chyle is swept very rapidly through the small intestine, as has been shown by Cannon (15) for the cat. Its speed is greatest in the duodenum and upper jejunum, giving time for little absorption, and while it slows down in the ileum, it should be past the ileocaecal valve in 4-5 hours. Once in the colon, the organism is safe, for the colon itself is comparatively impermeable to the toxin, and so remains. Closed loops of colon full of feces can exist almost indefinitely in man or animals, as the writer has found by experiment, and as many others testify (15, 20, 25, 26, etc.). The only danger is from distention, perforation and peritonitis. Kukula (41) describes a cat with a simple obstruction at the sigmoid, which lived in good health for several weeks. Even the lower ileum of dogs is much less active than the gut higher up, since dogs with closed ileum loops may live very long periods, *e. g.*, 550 days (20). In case of an ileus, continuous secretion with absorption of water would serve to concentrate the poison in the loop or above the obstruction. With copious vomiting, lavage, and infusions, the toxin would be removed and life might be prolonged (28).

At this point, however, serious objections to the theories of absorption by normal mucosa intervene. It has been seen that concentrated toxic substance when placed in contact with normal mucosa, is not absorbed.

Whipple (72) has shown that dogs may die with all the symptoms of obstruction, when a closed loop has been made and drained to the outside. There is no accumulation of fluid in such loops, and the mucosa appears normal.

The only inference which can be drawn from these facts is that, in obstruction and closed loops, a subtle change takes place in the mucosa—nothing is seen with the microscope, yet the cells in some manner discharge or allow to be discharged, the fatal toxin into the blood. It has been impossible up to the present to demonstrate any increased permeability of the mucosa to the toxic substance.

CONCLUSIONS.

This paper has shown that the duodenal and upper jejunal mucosa, unaided by bacterial action, and in conditions not far removed from normal, can produce a highly toxic substance, and that although phenolsulphonephthalein is readily absorbed by the normal mucosa of the small intestine, this toxic substance is not.

In closed loops one deals with a mucosa which displays nothing more than a slight hyperæmia, sometimes not even that. Injuries from handling are negligible, and absence of normal secretions from above is readily excluded as a cause of the mischief. Loop contents themselves in concentrated form will not stimulate absorption of toxin from the lumen in a freshly made loop. It seems clear, then, that some condition existing in closed loops causes slight but important functional changes in the mucosa, resulting in fatal toxæmia. But further investigation of the details of this change must be made.

I am indebted to Messrs. Harold S. Morgan and Roy E. Fallas for their assistance in a number of the experiments.

PROTOCOLS.

DRAINED DUODENAL LOOP.

EXPERIMENT 1.

Cat, D-39.—Maltese, female, middle sized. Operation Jan. 16, 1913, 3.30-6.00 p. m. Isolated duodenal loop, upper end brought to surface and sutured in a stab wound in right flank, lower end brought to surface and sutured in median laparotomy incision. Intestinal ends inverted, lateral duodenojejunosomy. Rubber drainage tubes inserted in each end of loop.

Jan. 17, 1913. Lies quietly in cage, but is strong and active when handled. Washed out with 200 cc. of warm water; washings slightly discolored, yellowish brown, very little solid material, few flakes mucus. Preserved with chloroform and toluol.

Jan. 18, 1913. Larger amount mucus and granular material to-day.

Jan. 24. Is being irrigated daily. Strong and bright, no toxic symptoms have been noted though loop ends are infected.

Jan. 26. To-day animal's appearance is entirely changed; sick and weak. Killed with ether. At autopsy, fresh peritonitis and failure of one of the intestinal blind ends, possibly due to a large piece of pig's aorta which cat has eaten, and which blocks up the duodenojejunosomy. Mucosa appears normal except for absence of bile pigmentation. Microscopic section of loop shows villi pressed together; epithelial cells appear healthy and active; many goblets. In the interstitial tissue which is not especially cellular are some places where there are small numbers of polymorphonuclears. No congestion or desquamation. Peritonitis, quite superficial.

About 1200 cc. of light brown, slightly turbid fluid had been collected in the 9 days. It was evaporated under reduced pressure at 60° C. to 115 cc., and filtered, giving a clear, slightly opalescent fluid with a slight, pleasant odor resembling that of beef broth. A more pungent odor resembling that of pentamethylendiamin, which had been present when washings were made, was driven off by the evaporation.

The fluid was given intravenously to a dog, D-65, male, weight 8 lbs., at 3.00 p. m., March 6, 1913. Kymograph record of B. P. and respiration made. Fall, then rise of B. P.; temp. at end of injection, 35.8° C. Condition seems good. 1½ hours later, animal lying on side, breathing rapidly, comatose. Pulse rapid, weak.

Profuse diarrhoea, not yet bloody. 8 p. m., animal dead (5 hrs.). At autopsy, splanchnic area congested. Intestines full, dark color. No peritonitis. On opening bowel, extreme congestion of mucosa is seen, beginning at pylorus, and involving entire small gut and colon. Distended with fluid contents, layer of mucus over epithelium. Blood dark, thick, does not clot readily. Microscopic preparation of duodenum shows tremendous congestion with desquamation of epithelium. No cellular infiltration or other signs of infection. This corresponds in every way with the picture described by Whipple in his dogs poisoned with closed dog loop fluid.

FISTULA.

EXPERIMENT 2.

Dog, D-66.—Large, black, male, weight 20 lbs. Operation March 8, 1913, 2-3.30 p. m. Intestine about 20-33 cm. below pylorus sutured to an opening in the skin, left rectus region. Fistula not opened. Second operation, April 3, 1913, 10-12 a. m. Bile duct doubly ligated, cut between ligatures. Pancreatic ducts tied and cut. Head of pancreas dissected away from duodenum. Fistula opened, tube inserted. Collection begun at 12 noon. On account of vomiting, little comes from tube, and the gut is irrigated with warm water. Total collection, 500 cc. turbid fluid, with flakes of mucus. Collection covers 6 hours.

Autopsy shows mucosa of duodenum slightly pink. In good condition opposite head of pancreas, except for hyperæmia. Fistula 55 cm. below pylorus. The fluid collected was at once mixed with chloroform and toluol and to it was added the mucosa taken from the intestine at autopsy.

The whole evaporated to 55 cc., and injected into jugular vein of dog, D-96, male, weight 11¼ lbs. April 11, 1913, 3 p. m. Dog was also given 2 cc. of a 5 per cent solution of peptone and 1/5000 gm. hirudin for another purpose, transient fall of B. P. only. Kymograph record of B. P. and respiration made. Evaporated washings caused no fall of B. P., slight acceleration of respiration. Temperature at end 37.9° C. Recovers quickly, vomits. At 8 p. m. (5 hrs.) animal is quiet, weak, drowsy. Lies on side, profuse non-fecal mucoid blood-stained fluid diarrhoea. Respiration rapid and labored. Temperature 40.8° C. Seems moribund.

April 12, 1913. At 9 a. m. dog is weak, but rather bright, now appears to be recovering. Diarrhoea is less, discharges now have fecal character. Appetite fair. Respiration still a little accelerated.

April 13, 1913. Dog has recovered. This animal had the typical symptoms, but evidently the dose was just sublethal.

EXPERIMENT 3.

Dog, D-71.—White, male, weight 27 lbs. Operation March 14, 1911. Intestine about 25 cms. below pylorus sewed to abdominal wall (1. rectus) for subsequent fistula.

April 14, 1913. Condition excellent. Second operation, 4-6 p. m. Bile duct tied and cut, pancreas dissected from duodenum, fistula opened. Condition seems good at end.

April 15, 1913. Dog in very fair condition. At 7.10 a. m. etherized, tube inserted in fistula, collection begun. Water is given by stomach tube to facilitate flow from intestine. It is pushed through gradually by peristalsis. In four hours, after 1¾ liters have been collected, the animal suddenly dies. The washings resemble those obtained in Experiment 2 and are treated the same way. At autopsy, the condition of all the organs is satisfactory except the stomach, which has been distended by introducing too much water. The intestinal mucosa appears normal. This time it is not added to washings.

The 156 cc. remaining after evaporation of the washings at 60° C. is injected into dog, D-105, female, weight 6 lbs., April 29, 1913, at 10 a. m., kymograph record of B. P. and respiration made. Primary depression of B. P., subsequent recovery. Temperature

at end 33.6° C. Recovers slowly from ether. At 3.30 p. m. (5 hrs.) animal is comatose, crying with each respiration. Temperature 27.5° C. Pulse soft. No diarrhoea. At 6.00 p. m., the same (7½ hrs.). At 10 p. m. (11½ hrs.), still comatose, breathing very quietly; cries, however, when touched. Body quite cold to touch, rectal temperature 21.5° C., which is just room temperature. Femoral pulse and apex beat imperceptible. No diarrhoea, vomiting or convulsions. Abdomen opened, gut is very full and purple. April 30, 1913, 9 a. m. Dead. No reaction about wound, probably died about midnight (13 hours). At autopsy, typical and extreme picture of poisoning; the congestion of the mucosa extends through entire small gut and involves colon; stomach is full of fluid; intestine distended with bloody fluid and mucus. Blood dark and thick, does not clot readily. The course of this animal was unusual. He behaved as other dogs for 7 or 8 hours, at the end of which time he was apparently at the point of death. That respiration should have continued after the body temperature became the same as that of the room, is remarkable. The absence of diarrhoea must, in the light of the autopsy findings, be attributed to paralysis of the intestinal musculature. This not infrequently occurs in these cases, but usually in animals dying 2-4 hours after injection.

EXPERIMENT 4.

Dog, D-14.—White, male, medium size. Operation May 19, 1913, 2-4.30 p. m. Bile duct tied and cut, pancreas removed entirely, beginning of ileum sutured to abdominal wall for fistula. Condition good at end. May 20, 1913, fistula opened at 9.30 a. m. A little water is given by stomach tube, but no flow ensues. A small dose of chloretone is placed in the intestine distal to the fistula, and ether cone removed. At 2 p. m., abdomen is opened, glass tube tied into pyloric end of stomach. Warm, weak salt solution is irrigated through the segment of intestine for eight hours. Washings caught in bottle containing toluol and chloroform. Dog remains alive but unconscious the next morning. Autopsy is performed. Mucosa of duodenum looks normal. Small amount of mucus upon it. No areas of injection or other abnormality seen. Microscopic preparation shows villi somewhat pressed together; otherwise nothing abnormal. Epithelial cells healthy, nuclei perfectly stained, no congestion, œdema, or cellular infiltration. Approximately 1½ liters of washings are evaporated in the air at 60° C. to 35 cc.

The resulting clear fluid is injected into dog, D-120, May 27, 1913, at 5 p. m. Kymograph record not taken. Pulse shows no marked depressor effect. Temperature at end, 37.8° C. Recovers quickly from ether. At 10.45 p. m. (5¾ hrs.), animal very badly poisoned, lies comatose, breathing is shallow, frequent, deep sighing respirations. Pulse soft, rapid, 132 per minute. Temperature 35.8° C. Large masses of bloody, tenacious mucus are being extruded from the bowel. Twitching of leg when stimulated. Practically moribund.

May 28, 1913, 9 a. m., dead and rigid. Autopsy: Typical but rather mild picture of poisoning. Congestion of intestinal mucosa begins sharply at pylorus. Bloody mucus in lumen. Diminishes in jejunum. Ileum appears practically normal. Colon, however, is markedly injected and contains bloody mucus. Bowel retains more muscular tone than is seen in the most severe cases. Stomach not injected. Blood dark and thick, clots slowly. In this experiment, salt solution was used in the irrigation instead of plain water, in order to avoid such a great upset of conditions of osmotic pressure in the intestine.

ABSORPTION OF TOXIN FROM CLOSED LOOP.

EXPERIMENT 5.

Dog, D-56.—Black and tan, male, weight 12¾ lbs. Operation Feb. 11, 1913, 11 a. m.-12.30 p. m. Closed duodenal loop, ends ligated with double heavy silk, closed in with running mattress

sutures of fine silk. 68 cc. of fluid, D-40-43, put into loop. Gastroenterostomy. Condition good at end. Temperature 35.3° C.

February 12, 1913. Dog much better, brighter, but vomits large amounts when he tries to eat.

February 13, 1913. Better, good appetite, still vomits occasionally. Remains in fair condition with some loss of weight, until February 18, when another operation is performed.

Autopsy: February 19, it is found that there is a slight leak at the lower end of the loop. 60 cc. of the fluid, D-40-43, which was from duodenal loops in cats, had previously killed a dog weighing 10¾ lbs. The dose then was a lethal one, but the value of the experiment is lost, through development of a leak in the loop.

EXPERIMENT 6.

Dog, D-137.—Black, female, weight 14 lbs. Operation July 23, 1913, 2.30-3.00 p. m. Closed duodenal loop, ends crushed and tied with double heavy silk, closed over with running mattress suture of fine silk. 52 cc. of fluid O, Dogs 86, 87, 91, 93, inserted into the loop through a needle. No gastroenterostomy. Condition good at end. 4.30 p. m. Has recovered from ether, but is very quiet. Vomits.

July 24, 1913. Walks about, wags tail, appetite poor.

July 26, 1913. Becomes very sick in afternoon, etherized 3 days after operation. Autopsy: General peritonitis from perforation of the loop, which has been distended. It cannot be said that this animal, who lived 72 hours, died any sooner than others into the loops of which nothing had been put. There was some hyperæmia of the mucosa of the unobstructed part of the gut below the loop.

EXPERIMENT 7.

Dog, D-138.—Male. Operation July 30, 1913. Closed duodenal loop, ends crushed and ligated with heavy silk, closed in with fine silk. No enteroanastomosis. Condition good at end.

Lived about 50 hours, dying at noon, Aug. 1, 1913. No diarrhœa. Autopsy, no peritonitis. Loop is almost empty, but does not leak. Contains 10-13 cc. soft, putty-like greenish-gray material. Mucosa appears quite normal. No injection of any part of small intestine. The contents of the loop of D-138 were put at once into a fresh duodenal loop made at 3.30 p. m., Aug. 1, 1913, in dog, D-139, weight 11½ lbs. The ends of loop of D-139 were also crushed, tied with heavy silk, and closed in with fine silk. No enteroanastomosis. The contents had been diluted with salt solution to a volume of 100 cc. Condition good at end.

Aug. 2, 1913, 24 hours after operation, runs about, pulse good quality, condition almost as good as before operation. No evidence of toxæmia.

The mucosa from the loop of D-138 was ground up with about 75 cc. salt solution, and put at once into a fresh duodenal loop made at 4.40 p. m., Aug. 1, 1913, in dog, D-140, weight 20¾ lbs. The ends of the loop of D-140 were also crushed, tied with heavy silk, and closed in with fine silk. No enteroanastomosis. Condition good at end.

Aug. 2, 1913, 24 hours after operation, runs about, pulse good quality. No evidence of toxæmia.

Whipple (personal communication) has performed similar experiments as 5, 6 and 7 with the same result.

With the exception of D-114, where chloretone was given, all operative procedures described in this paper were carried out under full ether anæsthesia.

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NATURAL IMMUNITY OF ANIMALS AGAINST POISON OF INTESTINAL OBSTRUCTION.

By DAVID M. DAVIS, M. D.,

Assistant in Pathology,

and

HAROLD S. MORGAN.

(From the Hunterian Laboratory of Experimental Pathology, The Johns Hopkins University.)

In the literature of intestinal obstruction, it will be found that the many investigators have used many different kinds of animals in their experiments, from hedgehogs to monkeys, and have attacked the problem from many standpoints. The apparently contradictory character of the conclusions drawn will be very bewildering to the reader. It is hoped that the present paper may explain some of these contradictions.

In the experiments leading up to their paper on intestinal obstruction, Whipple, Stone and Bernheim noted that in the few instances when they injected the toxic material, obtained from closed duodenal loops in dogs, into the veins of cats instead of dogs, the animals appeared to be resistant. The present writer then began to investigate this phenomenon.

The first step taken was an effort to produce a toxic material from cats in the same manner in which it had been produced in dogs; *i. e.*, by making a closed duodenal loop, with an enterostomy to shunt the intestinal current past the closed loop.

At first, the ends of the loop were tied off with silk thread, and a gastroenterostomy made. Three animals were operated upon thus, and the results were entirely unsatisfactory, since if any obstructions were produced, the animals readily survived until the ligatures cut through into the lumen, restoring continuity. In two the bowel between the sites of ligature was enlarged and thin walled, suggesting that at first, before the ligatures cut through, it had been distended by fluid. Later other ligature materials and wooden clamps were tried without success, and eventually the technique of choice became a loop about 12-18 cm. long with the ends sectioned, inverted, and carefully closed with a double row of sutures, and a lateral duodeno-jejuno-stomy. The upper end of the loop was invariably from 1.5-3 cm. below the opening of the bile duct.

In looking through Table I it will be seen that there is a good deal of discrepancy in the results. Peritonitis is a most frequent occurrence, whereas in dogs operated upon in the same manner, it is very rare. The cats with ligated loops invariably survived, barring peritonitis, until the ligature cut through, while this is rarely the case with dogs. One cat, No. 20, survived six days in good condition, finally succumbing to a perforation of the distended loop, while another,

No. 44, suffered the same accident in less than 48 hours. In others, as Nos. 63 and 75, the end of three days found the loops still collapsed, with mucosa appearing normal and containing a small quantity of pasty material. The properties of the contents of different loops vary in like manner, as will appear in Table III. The cause of these differences is not clear to the writer; for the present we must assume that mechanical factors, handling and the like, are responsible for the versatile activities of the mucosa. The behavior of the ligatures and the frequency of peritonitis are undoubtedly due to a lack of strength in the submucous coat of the intestine, as compared with that of the dog.

The average length of life of dogs operated upon by sectioning and inverting the ends of the loop is (Whipple) from 24-36 hours. The average time of survival of the 14 cats which were prepared thus and allowed to die spontaneously was 3.2 days, including all cases, with or without peritonitis. The increased resistance of operated cats is quite definite, but when the material obtained from the closed loop is injected intravenously into dogs and cats, the contrast is striking.

Table II shows the results of injecting toxic material into cats.

The material used in making these injections (Tables II-IV) was prepared as follows: Mucosa was scraped away from submucosa, and mixed with salt solution. The contents were diluted, if necessary, with .9 per cent salt solution. In either case, toluol and chloroform were added, the mixture placed in the thermostat at 37° C. and allowed to autolyze from 2 to 10 days. Just before injection, the material was heated for 30 minutes to 60° C., centrifuged if necessary, and filtered through several layers of filter paper with the aid of a vacuum pump.

Whipple, Stone and Bernheim have shown that the toxin obtained from dog loops is not destroyed by this treatment. The injections were made from a burette into the external jugular vein, and kymograph records of the blood pressure and respiration were made in a majority of instances.

In analyzing Table II, it will be seen that no death attributable to toxic action—barring the death on the table (No. 24)—occurred; and, indeed, that no symptoms, except a few

TABLE I.—CLOSED INTESTINAL LOOPS IN CATS.

No.	Loop	Anastomosis	Lived days	Autopsy		
				Loop	Contents	Remarks
2	Ligated, silk.....	Gastro-enterostomy.	20*	Ligatures leak freely.....	Normal.....	Etherized while in good condition.
3do.....do.....	4do.....do.....	General peritonitis; necrosis about ligatures.
4	Ligated, cord.....do.....	2	Distended, does not leak on light pressure; mucosa hyperemic, ecchymoses.	50 cc. thin, white fluid, granular.	Do
5	Ligated, silk.....do.....	4*	Distended, but ligatures leak; mucosa looks normal.	Thick, light yellow..	No peritonitis; etherized while in fair condition.
6do.....do.....	20	Distended, but ligatures leak; mucosa normal.	Dirty, mucoid, bile-tinged.	No peritonitis; intestines contracted, partial obstruction? Pneumonia.
7	Ligated, cord.....do.....	23	Leaks at lower end only; mucosa normal.	Gray, muddy.....	Ulcer with perforation and local peritonitis, just below gastroenterostomy.
8	Wooden clamps.....do.....	3	Not distended, mucosa normal, leaks into peritoneum.	Small amount, dark, clay-like.	Necrosis under clamps; general peritonitis.
9do.....do.....	2	Leaks into peritoneum; mucosa slightly injected.	Thin, gray, muddy..	Do
10do.....do.....	3do.....	Small amount, like pea soup.	Do
12	Ligated, cord.....do.....	17	Ligatures leak; mucosa normal; enlarged and thin walled.	Normal.....	Cause of death unknown.
14	Upper end, ligated, cord. Lower end sectioned, inverted.do.....	2	Upper ligature leaks into peritoneum; loop distended, mucosa reddened.	Thick, like pea soup, but red in color.	General peritonitis; necrosis about ligature.
15do.....do.....	12	At end of 10 days, laparotomy shows loop enlarged, thin walled, but ligature leaks. Retied. At autopsy, loop distended; no leak; mucosa reddened.	Large amount light brown material, like bean soup.	No peritonitis at 2d operation. At autopsy, beginning peritonitis due to eversion of cut end from pressure.
16do.....do.....	3	Slight leak to peritoneum upper end; distended, mucosa reddened.	35 cc. like pea soup.	Beginning peritonitis; slight necrosis under ligature.
17do.....do.....	3½	Distended, but leaks into peritoneum; mucosa injected.	Dark, almost black fluid.	Peritonitis; necrosis under ligature.
18	Upper end ligated tape. Lower end inverted.do.....	2½	Distended, but leaks into peritoneum; mucosa reddened.do.....	Do
20	Sectioned; inverted....	Oblique duodeno- jejunostomy.	6	Perforation; mucosa green, friable; hemorrhages, ulcers.	Dirty, black, syrupy.	Peritonitis following perforation.
21do.....do.....	2*	Distended, dark, no leak; mucosa injected, ecchymoses.	40 cc. greenish black, fluid.	Died under ether; fluid was to be withdrawn from loop.
23do.....do.....	2¾	No leak, distended, black; mucosa dark red, in places greenish.	50 cc. black, fluid...	Peritonitis; anastomosis leaks.
25do.....	Lateral duodeno- jejunostomy.	7	Loop excised, 2nd day; mucosa slightly reddened.	7 cc. dark brown, pasty.	No peritonitis at second operation; death from peritonitis due to failure of closed end of duodenum.
28do.....	Oblique duodeno- jejunostomy.	2¾	Distended; mucosa reddened.....	Green, like pea soup.	Beginning peritonitis over loop only; enteritis.
31do.....	Lateral duodeno- jejunostomy.	2¾	Distended; mucosa hyperemic, in places greenish.	Green, like pea soup. 75 cc.-50 cc.	Beginning peritonitis over loop only; 75 cc. withdrawn on 2d day, leaving loop very hyperemic.
35do.....do.....	4	Distended, no leak; mucosa injected..	50 cc. like pea soup.	Peritonitis from a leak in duodeno-jejunostomy.
40do.....do.....	2¾	Not distended, 35 cm. long; mucosa slightly injected.	20 cc., dark red, mushy.	Do
43do.....do.....	4	Loop leaks; mucosa slightly injected..	40-50 cc. like pea soup.	Peritonitis from leak at upper end of loop.
44do.....do.....	2	Gangrenous, perforation; mucosa dark, greenish friable.	50 cc. like pea soup.	Peritonitis from perforation, convexity of loop.
48do.....do.....	3	Distended, no leak; mucosa injected, dark.	40 cc. like pea soup.	Peritonitis from leak at duodenum, closed end.
54do.....do.....	3	Distended, dark; mucosa injected, no ulceration.	35 cc. like pea soup.	Slight beginning peritonitis over loop only.
63do.....do.....	3	Not distended; mucosa not injected or hemorrhagic.	4 cc. black, thick, semifluid.	Dry fibrinous peritonitis; origin?
70do.....do.....	2¾	Distended, no leak; mucosa dark, friable, no ulceration.	Large amount, like pea soup.	Peritonitis over liver only.
75do.....	None.....	3	Not distended, dark; mucosa dark, not injected or hemorrhagic.	Small amount, dark red, thick, like salve.	Slight beginning peritonitis over loop only.
79do.....	None.....	3	Notes lost.....
89	Ligated, silk.....	None.....	6-12 hrs.	Loop ———; mucosa appears normal.	Small amount, semi-fluid, dark brown.	No peritonitis; cause of death unknown.

TABLE II.—INJECTION OF LOOP FLUID INTO CATS.

No.	Fluid	From	Amount	Weight	Result
			cc.	gm.	
11	D4.	Duodenal loop, cat.....	25	No diarrhœa, quick recovery, no other symptoms.
	D2.	Normal mucosa, cat.....	35	
13	D8. 9. 10.	Duodenal loop, cat, contents and mucosa.	90	Slight transient fall in B. P.; quick recovery. No diarrhœa or other symptoms.
19	D16.	Duodenal loop, cat, contents and mucosa, separately.	66	Transient fall of B. P. Diarrhœa for $\frac{7}{8}$ hrs. after exp., then recovery.
24	3759	Human jejunal obstructions	11.5	Death on table; too rapid injection. This fluid is very toxic to dogs.
27	3759do.....	40	(Small.)	Recovers quickly; no symptoms. Death in four days; pneumonia and septicæmia.
30	D18. 21. 23. 25.	Duodenal loops, cat, mucosa.....	60	2048	Recovers quickly; no symptoms.
32	D31.	Duodenal loop, cat, contents.....	57.5	Recovers fairly well, but diarrhœa sets in next day. Death in 48 hours. Colon alone is injected. Section shows infectious colitis.
36	D15. 12. 20.	Duodenal loops, cat, contents.....	45	2560	Recovers quickly; no diarrhœa or other symptoms. See 37, Table III.
41	D26.	Normal mucosa, dog	56	2360	Recovers quickly; no symptoms.
67	D56.	Ileum loop, dog, contents and mucosa..	30	A little diarrhœa; recovers quickly.
			30	No diarrhœa or other symptoms. Intraperitoneal injection one day later.
69	D35. 44. 48. 54. 63.	Duodenal loops, cat, contents.....	50	2048	Some diarrhœa; green soft stools; vomits. After 4 hrs., no diarrhœa; or other symptoms; remains well.

Injections intravenous, except as noted.

TABLE III.—INJECTION OF CAT LOOP FLUID INTO DOGS.

22	D15. 17. 20.	Duodenal loop, cat, mucosa.....	115	5120	Death in 3 hrs.; typical picture at autopsy; profuse watery diarrhœa and vomiting antemortem.
26	D6-7.	Duodenal loop, cat, (leaky) contents and mucosa.	3460	Sick after injection, no marked diarrhœa, killed 5 days later; mediastinal abscess, extension from neck wound.
29	D18. 21. 23. 25.	Duodenal loop, cat, mucosa.....	60	3460	Vomited once, but no diarrhœa; recovery.
34	D-1.	Duodenal loop, cat, contents.....	40	4600	Prostration; profuse fluid; bloody diarrhœa; recovers slowly; killed 5 days later; has distemper.
37	D15. 17. 20.do.....	50	6660	Death in 4 hrs.; typical picture at autopsy; bloody, mucoid diarrhœa antemortem.
38	D18. 21. 23. 25.	Duodenal loops, cat, contents.....	100	5630	Sick, vomits, is prostrated, but no diarrhœa; recovers later.
42	D25. 27.	Normal mucosa, cat.....	58	5770	Death in $\frac{4}{5}$ hrs.; typical picture at autopsy; bloody diarrhœa and vomiting antemortem.
47	D31. 28. 35.	Duodenal loop, cat, contents and mucosa.	50	8960	Sick, but no diarrhœa; recovers fairly well.
49	D18. 21. 23. 25. 31. 28. 35.do.....	120	5740	Death in 5 hrs.; typical picture at autopsy; only slight diarrhœa antemortem.
53	Normal mucosa, cat.....	95	5000	No diarrhœa; quick recovery.
55	D40-43.	Duodenal loops, cat, mucosa and contents	60	5500	Death in $\frac{5}{10}$ hrs.; typical picture at autopsy; only slight diarrhœa antemortem.
62	D50.	Ileum loop, cat, contents and mucosa...	60	4100	Death in 44 hrs. There has been diarrhœa developing late, and lesions are atypical.
65	D39.	Washings from drained loop, cat.....	115	4100	Death in 5 hrs.; typical picture at autopsy; diarrhœa antemortem.
68	D35. 44. 48. 54. 63.	Duodenal loops, cat, contents and mucosa	50	4360	Death in 7 hrs.; typical picture at autopsy; bloody diarrhœa and vomiting antemortem.

Injections intravenous.

TABLE V.—NEUTRALIZATION OF LOOP FLUID WITH CAT MATERIAL.

No. dog	Fluid	From	Neutralizing agent	Stood days	Amount	Weight dog	Result.
					cc.	gm.	
52	D18. 21. 23. 25. 31. 28. 35.	Duodenal loops, cat, contents and mucosa. 85 cc.	Normal cat serum. 53 cc.....	1	127	4860	Sick, but recovers, diarrhœa not marked.
73	D35. 44. 48. 54. 63.	Duodenal loop, cat, contents and mucosa. 60 cc.	1 spleen and small piece of liver, normal cat..	4	75	4350	Death in 6 hours, typical lesions at autopsy. Severe diarrhœa.
74do.....do.....	Spleen from two normal cats.....	4	75	3740	Do.
77do.....do.....	250 cc. whole blood, normal cats; coagulum ground, fluid filtered.	13	230	3585	Death in 5-8 hours, typical lesions at autopsy. Severe diarrhœa.
107	W.....	Duodenal loop, dog, contents. 30 cc.	Liver, spleen and intestinal mucosa of 2 normal cats.	7	300	7170	1 soft stool. Recovers, but seems sick; dies in 48 hours; autopsy picture of septicæmia.
132	O86. 87. 91. 93.	Duodenal loop, dog, contents. 54 cc.	108 cc. filtered autolysate of normal perfused liver, spleen, and intestinal mucosa of cat.	10	162	6912	Death in 8 hours, typical lesions at autopsy. Severe diarrhœa.
135do.....	Duodenal loop, dog, contents. 50 cc.	105 cc. fresh filtered autolysate of normal perfused liver, spleen, pancreas, and intestinal mucosa of cat.	7	112	6150	Death in 6-9 hours, typical lesions at autopsy. Severe diarrhœa.
	Controls.						
133	None.....	115 cc. autolysate liver, spleen, and intestinal mucosa, normal cat.	...	115	6660	Diarrhœa, death in 7 hours. Picture atypical; scattered areas of hyperemia in mucosa.
136	None.....	85 cc. autolysate normal perfused liver, spleen, pancreas, and intestinal mucosa of cat. Same as used with No. 135.	...	85	5632	Quick recovery, no diarrhœa or other symptoms.

soft stools and some vomiting, were elicited. Cat, No. 31, died with severe diarrhoea, but it developed rather late, and microscopic examination showed an oedematous colon mucosa, heavily infiltrated with polymorphonuclear leucocytes, and alive with bacteria. The process extended, in a milder degree, some distance into the ileum.

Table III gives the results when toxic material was injected intravenously into dogs.

It also shows that the fluids obtained from different animals of the same species, operated upon, as nearly as possible, in the same manner, may differ greatly in toxicity. The fluids used with dogs, Nos. 29, 38 and 47, were resisted in ordinary doses, but when combined and a large dose given, they proved fatal to dog, No. 49. Dogs, Nos. 37, 55 and 68, however, succumbed to moderate doses. Dogs, Nos. 37 and 68, were injected at the same time as cats, Nos. 36 and 69. The results are placed side by side in Table IV.

TABLE IV.—IMMUNITY OF CATS TO POISON OF
CLOSED LOOPS.

No.	Fluid from cat duodenal loops	Amount	Weight	Dose per gm. in cc.	Species	Result
		<i>cc.</i>	<i>gm.</i>			
36	D15. 17. 20.	45	2560	0.0180	Cat	Recovery, no symp- toms.
37	D15. 17. 20.	50	6660	0.0075	Dog	Death in 4 hours; typical lesions.
69	D35. 44. 48. 54. 63.	50	2048	0.0240	Cat	A little diarrhœa; recovery.
68	D35. 44. 48. 54. 63.	50	4360	0.0114	Dog	Death in 7-8 hours; typical lesions.

Intravenous injections in each experiment.

In each experiment (Table IV) the cat received more than twice as much poison, per gram of body weight, as the dog, and in each case, it recovered easily, while the dog succumbed. It would have been desirable to push the dose to the lethal line for cats, but the supply of material was insufficient.

The results in the above tables were taken to show that dogs reacted to the toxic substance produced in closed loops of cats in the same manner in which they react to that from closed dog loops. This reaction is described by Whipple, Stone and Bernheim,¹ and is in brief as follows: At the time of injection, the blood pressure shows a transient fall, and respiration is accelerated. The animal recovers from ether and, if not too strongly poisoned, walks about and seems fairly normal. Diarrhoea may begin at any time; soon, usually in about 1½ hours, the animal grows quiet, a slow but steady fall of blood pressure and temperature commence, diarrhoea increases, becoming mucoid, then fluid and bloody, copious vomiting occurs, coma intervenes and death takes place in 4-8 hours, with convulsive muscular twitchings and paralysis of respiration. There may be slight variations, as; for instance, if the dose is overwhelming, the animal may succumb in 2-4 hours without vomiting or diarrhoea, when the bowel

and stomach will be found tightly distended with bloody fluid which has not had time to find an exit.

The autopsy findings, which are designated in the tables as "typical lesions" are quite constant. The appearance is that of great splanchnic congestion. The veins are full, the intestine and stomach distended and dark colored, the peristaltic movements active. On incising the stomach, it is full of fluid and mucus, which may be blood-stained. The gastric mucosa may show slight hyperemia, but never a very marked grade. Beginning, however, at or slightly below the pylorus, the intestinal mucosa shows the most extreme hyperemia and swelling, and is covered over with a thick, buttery layer of yellow mucus. The lumen is filled with a thin, blood-stained fluid. The normal bile-stained color of intestinal contents is entirely lacking. This turgidity of the mucosa is most pronounced in the duodenum. It is always uniform, never patchy. In mild cases, it may extend downward only to the upper jejunum, while in severe cases it involves duodenum, jejunum, ileum and colon in an almost uniform congestion. If diarrhoea has existed for any length of time, everything resembling normal contents or feces will have been expelled, and nothing remain in the gut except the watery, blood-stained, choleraic fluid with flakes of mucus described above. The heart usually stops in diastole, though it may beat for some time after respiration ceases. The blood is very dark and thick from its dehydration, and clots with great slowness. This last phenomenon is due, according to Whipple, to the presence of an excess of antithrombin. Microscopically the mucosa shows tremendous swelling, distention of the blood vessels and extravasation of blood. There is an enormous amount of epithelial desquamation, but no polymorphonuclear infiltration or other sign of infection.

All these details were observed in the dogs poisoned with cat material, and therefore it would appear that the toxic substance present is probably similar to that found in the closed loop of dogs. Dogs seem to have a tendency to react in this manner, witness the similar, but not identical, pictures in "anaphylactic enteritis" and poisoning with typhoid and colon bacillus toxins.^{2 3 4}

In Table IV, animal, No. 42, is shown as being fatally poisoned by an extract of normal cat small gut mucosa. Since the material had stood some time, however, and since a later experiment with fresher material (No. 53) failed to support the finding, it is not thought to be of great importance. Why the first-mentioned extract should have been or have become toxic is not at present evident, though the conjecture of a possible secretion of toxic substance by normal or apparently normal mucosa at once presents itself.

In Table III, again, animal, No. 65, was killed in a few hours, with symptoms and autopsy picture the same as in those poisoned with closed loop material, by a fluid which was obtained by daily washing out a cat duodenal loop which had been brought to the surface at each end. This cat, D. 39, remained in excellent condition during the time the loop was irrigated daily. The secretion was in the form of almost clear, slightly yellowish fluid, containing flakes of mucus. It was

immediately preserved with chloroform and toluol, and evaporated down at 60° C. to suitable volume for injection. Here the poisonous material was removed as it formed from the segment of gut, and the cat did not show the effects of its absorption. The mucosa of this drained loop at the end of the experiment was macroscopically normal.

The reader will have noted that the toxicity of the various cat loop fluids has been judged in this paper solely by their action on dogs as experimental animals. Efforts were made to discover some smaller animal which would be suitable for this purpose. It was felt that any mode of injection except the intravenous was unsatisfactory, owing to the difficulty in sterilizing the fluids, and the somewhat irritant nature of some of the extracts.

Guinea-pigs, rats and mice were abandoned. Other observers have found guinea-pigs so susceptible to foreign materials as to render them useless.⁵ A long series of injections was made in 35 rabbits with the result that they, too, seem unsuitable for the purpose. Their hold on life is very insecure, and they readily succumb to infection, intercurrent or even preëxistent disease. A rabbit infected with coccidiosis will die from a much smaller dose than will be sustained by its uninfected brother. Unless the greatest care is exercised in injection, the animal may die in convulsions in a few minutes, while if it does not, it often lives 24-48 hours, when the possibility of infection spoils the result. When death does occur in a few hours, no typical symptoms have been noted, and the autopsy findings are indefinite. All this is in contrast to dogs, which readily resist the infection from injections of non-toxic fluid, but which die with remarkably constant symptoms, and which present a typical picture at autopsy.

Drained loops like that described above, known as Vella loops, have long been used by physiologists in investigating the intestinal secretions. It has been noted by some of them that if a second dog receives an injection of the contents of such a loop, he himself is better able to withstand the creation of a similar loop of his own intestine. Whipple, Stone and Bernheim demonstrated the existence of an immunity of this sort in dogs—when treated with ascending doses of toxic material they support a lethal dose of toxin intravenously, and also live much longer than otherwise after a closed loop has been made. The researches of these investigators show that the immunity in these animals resides principally in the liver, spleen and intestinal mucosa, and not at all in the blood.⁶ Since it appeared that in the cat we possess an animal enjoying a natural immunity, it became of interest to discover, if possible, wherein that immunity lay. With this intention, various known toxic fluids, principally from dog closed loops, were mixed with organs from normal cats, with cat whole blood, and with cat serum, allowed to stand for some time in the incubator, and then filtered and injected into test animals (small dogs).

Table V shows that little success was attained in these efforts. Two of the dogs, Nos. 52 and 107, did not die typically. In the case of dog, No. 52, the toxic fluid used was of doubtful potency. In the case of dog, No. 107, some dog loop fluid,

kindly furnished by Dr. Whipple, was used. Previous tests had shown that 10 cc. of it would kill a dog weighing 15 lbs. (7680 gm.). This fluid was incubated with a large quantity of ground cat organs, and part of it may have remained by absorption with the residue on the filter paper. Consequently, although this animal did not die a typical toxic death, one is not justified in considering it an unequivocal demonstration of neutralization of the toxin. In later experiments, the filtered autolysate of the organs was used instead of the ground organs themselves.

The death of the first control dog, No. 133, is confusing, but the fluid was rather old, and was of a lot not used in any of the neutralization experiments. It may have undergone bacterial change. In the case of dog, No. 136, the same fluid used in preparing the toxin-neutralizer mixture for dog, No. 135, was selected, and the injection of a large quantity of it had no effect whatever on the animal. Within two hours he was entirely normal, and making the most vigorous efforts to break down the door of his cage.

These experiments, then, remain rather inconclusive. But it is safe to say that closed loop toxin cannot readily be neutralized by autolysates of normal cat organs, as it can by autolysates of immune dog organs.

TABLE VI.—IMMUNIZATION OF RABBIT; DOG LOOP FLUID.

No.	Date	Dose	Weight	Dose per gm.	Result
		cc.	gm.	cc.	
112	5/17	3.1	690	.0045	Well.
	5/18	5.1	690	.0072	Well.
	5/22	10.2	690	.0148	Well.
	5/2	15.0	690	.0217	Well the same day, but dies in 48 hrs.; infection (?)
109	5/17	1.6	1640	.0010	Well.
110	5/17	1.3	640	.0020	Well.
111	5/17	4.5	1500	.0030	Dies in 2 hrs.; autopsy shows much mucus in intestine, also broncho-pneumonia.
113a	5/20	1.5	765	.0020	Well.
113b	5/20	2.5	620	.0040	Well.
113c	5/20	3.9	650	.0060	Sick, recovers at first; dies in about 12 hrs.; few small red spots in duodenum.
113d	5/20	5.6	695	.0089	Soon recovers; dies in 8-10 hrs.; many small red patches in intestine; but there are small areas of broncho-pneumonia.

Fluid used: O33-34, from closed duodenal loops of dogs.

Table VI illustrates the doubtful character of the results obtained with rabbits. If rabbits, 113 C and D, died from the effects of the toxin, rabbit, 112, undoubtedly had been given an active immunity; but it is not certain that they did. Therefore no definite statement can be made concerning immunity against closed loop toxin in rabbits.

From these tables it will appear that great care must be exercised in interpreting the results obtained by introducing

supposedly toxic intestinal material into animals of various species. In going through the literature, one finds that all experimenters have had difficulty in poisoning cats with intestinal toxins. Usually where they have succeeded, it has been by intraperitoneal injection, with lethal result in 14-18 hours, in which case the possibility of infection must enter. Von Albeck is an exception. He was able to induce the death of kittens by the introduction, intravenously as well as intraperitoneally, of 5-20 cc. of the contents of strangulated intestinal loops, suitably diluted with water. Some of them died in as short a time as $4\frac{1}{2}$ hours. He, however, states that many kittens and cats proved extremely resistant.⁷

Another source of confusion lies in the ease with which animals of any species may be killed by introducing this sort of fluid too rapidly into its veins; for example animal, No. 24, in Table II. It is, however, especially important in the case of rabbits, and mars the value of the work of Roger and his associates. In their results, all except immediate deaths are ignored, and it is only by perusing their tables carefully that one learns that some of the animals succumbed at the end of 5-24 hours, often with diarrhoea.⁸

CONCLUSIONS.

1. Cats will survive two to six days after the production of closed duodenal loops, often dying of peritonitis.

2. The contents of these loops after heating and filtration, will kill dogs, when injected intravenously, with the same symptoms and anatomical picture seen when dog loop contents are used.

3. Cats are resistant to this toxic material, withstanding with ease doses of over twice as much per gram of body weight, as is necessary to kill dogs.

4. Efforts to neutralize the toxin of duodenal loop contents by incubation with cat organ extracts, cat blood, and cat serum, have been unsuccessful.

5. Rabbits and guinea pigs are much less suitable for testing the toxicity of intestinal fluids than dogs, owing to their great susceptibility to hurtful influences of all sorts.

6. Cats are also less suitable for the same purpose than dogs owing to their high natural immunity against closed loop toxin.

The last two considerations must receive careful attention in drawing conclusions from any set of experiments dealing with the poisons of intestinal obstruction.

We are indebted to Mr. Roy E. Fallas for his assistance in a number of the experiments.

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NIELS STENSEN.*

By WILLIAM SNOW MILLER, M. D.,

(Anatomical Laboratory, University of Wisconsin, Madison, Wis.)

Pulchra sunt quae videntur, pulchriora quae sciuntur, longe pulcherrima quae ignorantur.—STENSEN.

Situated below and in front of the ear is the largest of the salivary glands. Extending from its anterior border, at its most prominent part, is a duct which opens into the mouth cavity by a small orifice opposite the second upper molar. This is the *ductus parotideus*, commonly known as the duct of Steno, or Stensen's duct.

As one wanders through the University of Copenhagen one will see hanging on the wall, surrounded by many of the old anatomists, a picture of a Catholic bishop. His curiosity is aroused by seeing a churchman placed in such strange company. The picture is that of Niels Stensen.

In the fall of the year 1881, the president of the International Congress of Geologists, then meeting at Bologna, sent a delegate to Florence to lay a wreath on the grave of a man who is considered one of the great men in the history of geology. The grave is that of Niels Stensen.

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How comes it that the man, who lies in that quiet tomb of the Medici in the Basilica of St. Lawrence at Florence, has his name connected with so varied a life as is indicated by the above statements?

I shall not attempt to answer in full the above question, for it would take more time than I have at my disposal. I shall confine myself largely to the anatomical side of the question referring to the rest sufficiently for a full understanding of the character and motives of our anatomical-geological-bishop.

Steen Pedersen, Stensen's father, was a goldsmith in Copenhagen; his mother was Anna Nilsdatter and was probably the second wife of Pedersen. On the 10/20 of January, 1638, there was born to the couple a son, who, as was the custom at that time, took the Christian name of his father. Besides a brother, 22 years old, by the name of John, Stensen had a sister, Anna, who married a certain Jacob Kitzero and lived at Copenhagen. Stensen's father died before he was six years old and, as his mother soon married again, he lived with his grandparents. In regard to this period of his life Stensen's

remembrances were not very pleasant, for from his third until his sixth year he was sickly, and, living as he did with his grandparents, he had too much of "old folks" and too little of the companionship of children of his own age. The conversation to which he had to listen was largely of a religious nature and, as Foster says, he "heard much, too much perhaps, of the doctrines of Luther."

We know but little of the early education of Stensen. Blondel states that his grandparents provided him with a private tutor in order to fit him for the university. However his early education was acquired it must have been very thorough, for in later life he spoke and wrote Latin, German, Dutch, French, Italian and English. He also had a fundamental knowledge of Hebrew and Greek. He was especially fond of mathematics, and had not circumstances directed him otherwise, would probably have made them his life study.

The University of Copenhagen was founded by Pope Sixtus IV in 1475, and the first instruction was given in June, 1479. At this time the university was under the auspices of the Catholic church and so continued until the Reformation, when, after various vicissitudes, it was discontinued in 1533. In September of 1537 Christian III restored the university as a Lutheran institution.

In 1656, at the age of 18, Stensen entered the university, or, as they said at that time *deponirte*. The word *deponiren* has quite another significance than "matriculation"; it refers to the highly grotesque and not always agreeable ceremony which took the place of the simple matriculation of the present day.

Within a specified time the young student, after depositing his school certificate, and it had been found satisfactory, had to present himself to the oldest *pedell* (who was always one of the oldest students) to be prepared for the academic consecration. On the appointed festive day the candidate appeared, with other candidates, at the *Studienhof* in a true carnival costume. The more grotesque it was the more pleasing it was to the student body. The *pedell* then came on the scene clothed in like manner and provided with whip, pinchers, plane and like instruments. He then drove the victims with shouts and blows into a room where a sort of examination was held; but no matter how well the questions were answered it always ended with a flogging.

Next they were subjected to all kinds of comic tricks with plane and pinchers and were pushed about until they were completely relieved of their clothing. Water was now and then dashed over their heads in order to remove the black smudge from their faces. When this was accomplished the students were *deponirt*. The "freshmen" then appeared before the dean of the university in proper clothing. One of them besought him, in the Latin language, for admission into academic citizenship in order that they might become fitted for a nobler and purer life than they had hitherto led.

The dean commended their zeal and explained in a long discourse, the symbolic significance of the preceding ceremonies. The flogging should recall the miserable school life from which they had now escaped, and at the same time

should prepare them for all the hardships that awaited them in the future which should be endured with the same patience as the blows of the *pedell*. The outlandish costumes in which they had been clothed should bring before them the crude, animal condition to which one brings himself before reaching the perfected strength of academic culture; the costume just cast off should encourage them to overcome every vice to which human nature is heir and to cultivate every virtue which improves and beautifies life.

At the close of the address the dean poured wine over the heads of the young students to express thankfulness that God had called them to a higher career, and then placed salt on their tongues as a symbol of wisdom, for which they should now strive of their own accord, nor longer be driven by rod or whip.

It was the custom at the University of Copenhagen for students to choose one of the professors for his preceptor, who should be his guide, philosopher and friend throughout his new scientific career. Stensen chose Thomas Bartholin, who preserved in him a student who eclipsed his own fame. This is a strong statement when one considers that the Danes to this day are exceedingly proud, and with good reason, of the family of Bartholin, who not only taught at Copenhagen throughout the entire seventeenth century, but, through their students, brought to their university a fame which extended over all Europe.

Under the direction of Bartholin, Stensen began the study of anatomy and at the same time he continued his earlier studies. He pursued with special industry not only mathematics but also Hebrew, in which he had already made considerable progress, and became so proficient that in later life he could easily read his Bible in that language.

The years during which Stensen was at the University were stormy. In 1658 the Swedes invaded Denmark and besieged Copenhagen. The students rallied to the defence of the city and formed a regiment which numbered 266 and was known as "the black coats" on account of the color of their clothing. Upon the roster of this regiment we find the name of Stensen; he held a commission as corporal with 86 students under his charge. Day and night they labored repairing the walls or repelling the attacks of the foe. This was quite another life than bending over his books or listening to the lectures of his professors. The patriotism of the Danish students has often been tried; in 1700, 1716, 1801 and 1807 they came to the defence of their beloved city.

Not only did the city have to contend with foes without, but they had an even more deadly foe to contend with within the city; famine broke out and they suffered all its horrors before relief came in the shape of reinforcements and provisions furnished by the Dutch fleet.

Though it be true *inter arma silent musae* Stensen found time to attend such lectures and to make such dissections as were conducted by his professors during the intervals when the students were not on duty.

After three years' residence at the University of Copenhagen it was the custom for students to complete their

studies at some foreign university, and their preceptor gave them a certificate and often letters of introduction to some special friend or colleague. Thomas Bartholin gave Stensen such a certificate and a letter of recommendation to Professor Gerhard Blasius of Amsterdam.

At the beginning of the seventeenth century the medical schools of Holland enjoyed a great reputation because of the advantages which they possessed in the teaching of anatomy and because of the men who taught anatomy: at Amsterdam was Blasius or in Dutch, Blaes; at Leyden were van Horne and Sylvius. Stensen pursued his studies at both of these places. Stensen first went to Amsterdam and became an inmate of the house of Blasius. Scarcely had he taken his scalpel in his hand when he made a discovery which will perpetuate his name—the discovery of the duct of Steno. No sooner had he made the discovery than he was involved in a controversy with Blasius. At that time discoveries in anatomy led to very acrimonious strife and, in the case of Wirsung, to murder. We have a very complete account of the controversy and it may be of interest to follow it, for it sheds light on the methods of the day.

Stensen himself, in a very modest way, gives an account of the discovery, in a letter which he wrote from Leyden, April 22, 1661, to his old preceptor Bartholin at Copenhagen. I will quote part of the letter:

Since you request of me in your letter to publish a representation of the external salivary canal, I am induced to explain to you briefly the envy which this otherwise unimportant discovery has caused me, as also the lessons which I have learned from it, not in order to seek glory in little things but to refute the hated accusation that I am anxious to adorn myself with borrowed plumage.

It is not a year since I was hospitably received by Blasius. He permitted me at my request, to dissect with my own hand whatever I should purchase, and fortune so favored me that in dissecting in my first study, the head of a sheep, which I had purchased on the 7th of April, I discovered a canal, which, so far as I know, no anatomist has as yet described. As I was just about to separate the well known tissues and then to dissect the brain, it occurred to me that I ought to first examine the vessels which surround the cavity of the mouth. While I was examining for this purpose the veins and arteries, I noticed that the point of my knife no longer wedged in between the tissues, moved more freely in a large cavity, and I soon heard as I pushed forward the iron the sound it produced by striking the teeth. Astonished at this discovery I called the master of the house to get his opinion. He first ascribed the sound to the thrust of the knife, then he had recourse to explaining it as a "freak of nature"; finally, he consulted Wharton, but since this also did not help us, and since the vessels, which had not been very carefully handled, did not permit of further examination, I determined to again make the same examination but with greater care. I succeeded, though not as well as the first time, on the head of a dog.

In the same month Stensen communicated his discovery to his friend Jacob Henry Pauli, who in 1662 was made professor of anatomy at Copenhagen, and later to Sylvius, better known as Du Boe or Dubois, at Leyden. Sylvius found the duct in man. In a letter to Eysonius of Groningen, the younger brother of Blasius ascribes the discovery to Stensen. Blasius, the elder, did not agree with him. He was greatly

enraged that Stensen should claim the discovery which he declared he himself had made. Instead of bringing proof that the discovery was his, he called Stensen "liar," "blasphemer" and "malevolent fellow inflated with envy." Good proof that Stensen's assertions were true. Further on in his letter to Bartholin, Stensen says:

Had not the celebrated Mr. van Horne given my name to the canal in so conspicuous a place, before such a circle of learned men, I should gladly have renounced my rights. But to proceed to other things: I shall mention one fact which I consider the most conclusive proof. Blasius shows plainly in his treatise "*De medicina generale*" that he has never sought for the duct; for he does not give to it either the proper point of beginning or ending, and assigns to the parotid gland so unworthy a function, that of furnishing warmth for the ear, that were I not right certain to have shown him the duct, I should be tempted to assert that he had never seen it.

Bartholin replied to this letter on the 10th of the following May, and says among other things:

The fatherland congratulates itself upon such a citizen, I upon such a pupil, through whose efforts anatomy makes daily progress and our lymphatic vessels are traced out more and more. You divide honors with Wharton, since you have added to his internal duct an external one, and have thereby discovered the source of the saliva concerning which many have hitherto dreamed much, but which no one has (permit the expression) pointed out with the finger. Continue, my Steno, to follow the path to immortal glory which true anatomy holds out to you.

Bartholin regretted the controversy that had arisen with Blasius. Probably his own controversy over the discovery of the lymphatics, which occurred about this time, made him somewhat cautious.

The annoying experiences to which Stensen was subjected at Amsterdam made his stay there disagreeable; besides he had outgrown Blasius. He therefore went to Leyden where Sylvius and van Horne taught. The ill will of Blasius followed him. Ole Borch, a fellow student of Stensen's at Leyden, wrote to Bartholin on the 20th of March, 1661, that he had heard that Blasius claimed the discovery of Stensen as his own.

But Stensen will answer him, not on account of the glory which is attached to the discovery, but because Stensen will not wish it to appear as though he had misled Sylvius and van Horne, who have publicly called the duct "Steno's duct."

About this time Blasius published his "*De medicina generale*," above spoken of, in which he expressly claimed the discovery of the duct. This claim Stensen proceeded to refute. On the 6th and 9th of July, 1661, Stensen conducted a brilliant public debate, over which van Horne presided, which did great honor to a young man only 23 years old. The debate increased the bitterness of Blasius and he complained in a letter written on the 16th of July to Bartholin, that Stensen takes to himself, regardless of propriety and in violation of the truth, a discovery the glory of which belongs to him—Blasius. Bartholin, although he did not openly take sides, answered Blasius on the 1st of September and called his attention to his ridiculous behavior. "Your con-

science will tell you who is right in this matter." "Farewell," he concludes his letter, "and control yourself."

In the mean time Stensen proceeded to investigate the glands of the eye. After he had returned from a short journey he reported the results to Bartholin, on the 12th of September. Bartholin rejoiced greatly over the success of his pupil, and wrote him on the 10th of November, "Your fame grows from day to day. Your pen and sharp eyes know no rest." Bartholin was right. Stensen worked incessantly and made discovery after discovery. In December he published the results of his work on the glands of the eye and vessels of the nose and, in the early part of 1662, this was followed by a collection of his observations.

Greatly elated by the progress of his student, Bartholin hastened to heartily recommend him to the King. "You may count upon the favor of the King, as well as the applause of the learned," Bartholin wrote Stensen on the 14th of February.

During the latter part of 1662 and in 1663, Stensen seems to have been busy with his investigations on muscle, especially that of the heart, and defending himself from the attacks of Blasius. On March 5, 1663, he wrote Bartholin that the controversy had again broken out; yet in the mean time Blasius had not learned where the canal began or ended.

In the early part of 1664 Stensen went on a short journey. Where he went no one has been able to discover; but on his return he went to Copenhagen. It is quite probable that the death of his step-father which occurred at this time called him home; possibly the prospective appointment as professor of anatomy was another reason. During his stay in Copenhagen he published his "De musculis et glandulis observationum specimen," which he dedicated to King Friedrich III. His conception of the heart as a muscle created the greatest sensation.

The heart has been considered the seat of natural warmth, as the throne of the soul and even as the soul itself. Some have greeted the heart as the sun, others as the king; but if you examine it more closely, one finds it to be nothing more than muscle.

Imagine the consternation this simple statement made; de Hedoville writing in 1665, says: "This simple observation overthrew a system to which medicine clung most tenaciously"; the celebrated physiologist, Haller, writing in 1774, did not hesitate to pronounce this volume a golden book which contained the rich seed for new discoveries.

In spite of Stensen's success as an anatomist and the great reputation which he had acquired, and notwithstanding the support of Bartholin, he failed to receive the appointment as professor of anatomy at Copenhagen. On the 29th of August the King appointed Matthias Jakobsen to the professorship, and Stensen hastened to leave the city.

He first went to Holland and then by the way of Köln to Paris where he remained until the end of 1664 or the beginning of 1665. The acquaintance which Stensen made while in Paris with Thevenot had a far reaching influence. Through him he gained entrance to the circle of savants who assembled about Thevenot. An address which Stensen gave before this

select circle, on the structure of the brain, attracted much attention. Not only his contemporaries, but also students of our own time acknowledge the important bearing of his address on the development of neurology. Both Daremberg and Sprengel declare it the beginning of modern investigations concerning this organ. I will quote a single paragraph:

Upon its surface you note many things which excite your wonderment, but after you have penetrated deeper you see nothing at all; all you can say is that you find there two different substances, the one grey, the other white; that the white substance is continued into the nerves which are distributed throughout the entire body; that the grey substance serves in some places as an envelope for the white, in other places it separates the white fibers from each other. If we ask what this white substance may be, in what manner the nerves are united with the white substance, how far the nerves penetrate with their furthest ends into this substance, we have reached a point where we must confess our ignorance, lest we desire to increase the number of those who prefer to be admired by a credulous public.

The entire address is well worth careful reading by one interested in the subject; it can be found in Winslow's "Exposition anatomique de la structure du corps humain."

In the fall of 1665 Stensen made a journey into southern France where he found the recommendation of Thevenot secured for him the friendliest reception among the savants. With Italy so near he could not pass by this land which was so interesting to the young scientist. A letter of Malpighi tells us that in the early part of May, 1666, Stensen was in Rome. From there he traveled by the way of Livorno to Florence where he remained some time perfecting himself in the Italian language.

There still remained some of the glamor of the ancient splendor of Tuscany. Even in Stensen's time the court of the Medici was the gathering place of the learned who visited Italy. The Grand Duke Ferdinand II, as well as his brother Prince Leopold, were the generous patrons and promoters of the sciences. Not only was Stensen kindly received by the Grand Duke, but through the influence of Thevenot, and of Viviani the pupil and companion of Galileo, he was appointed body physician to the Grand Duke who assigned to him a pension and a residence. Besides this Stensen received an appointment to the Hospital of Santa Maria Nuova. This interesting hospital was founded by Folco Portinari, the father of Dante's Beatrice, in 1288, and is still in existence.

Stensen now followed the court which held residence sometimes in Florence, sometimes in Pisa, sometimes in Livorno. During these journeys he had the best of opportunities to make observations and discoveries. A series of dissertations which he sent to Bartholin enabled him in the following year (1667) to publish a large epoch-making book on the muscles.

Stensen had at this time reached the height of his fame. Denmark now desired to have the young scientist occupy the chair of anatomy at Copenhagen; the savants of Holland and France admired his discoveries; Florence desired to entwine his laurels in her wreath of glory. Certainly, now that Stensen had become a Catholic, opportunities and honors came to him; but earthly motives no longer actuated him.

This brings us to an exceedingly interesting period in the life of Stensen; his conversion from Lutheranism to Catholicism. I wish I had more time in which to discuss this change in his life and work. I do not believe with Foster that it was a sudden change, but rather one that was reached after mature deliberation. Science lost a most brilliant worker, but the Church gained an earnest, lovable devotee who spared no effort to promote her interests.

When 21 years old Stensen left the university of his fatherland a faithful Lutheran. With impetuosity and vigor the young man gave himself up completely to the scientific current which met him in Holland; in scientific relations truly it was not to his disadvantage. Not so fortunate was the new atmosphere for his orthodox belief. Many of his friends were atheists, others, as Spinoza, pantheists; the greater number belonged to the motley crowd of Calvinists. Stensen soon became aware of the danger which threatened him from fellowship with such men. The study of the heart and other portions of the body had, so Stensen wrote a friend in Hannover in 1680, brought him back on the right track, since he had become convinced that so wonderful a structure could not arise by accident or fate but must be the work of a master workman whose wisdom was unending. As such he found God, the Creator of all things. His scientific studies carried him still further. The discovery of numerous errors which men of science advanced as established truths, shook powerfully his belief in his "infallibility" in religious things. Still more, and certainly forever, was his faith in the teachings of the Reformation shaken. Thus, step by step, he no longer held to the tenets of his father, no longer to his former dogmatism. This showed itself especially when he met with Catholics. Generally he abstained from discussing religion with them. If he could not prevent it, he defended himself bravely, as he said, so long as he held Luther's translation of the Bible and Catechism as the true, undoubted word of God. Still he could not conceal from himself that the life of some of his Catholic friends made a deep impression on him, a life which he neither found in philosophy nor had opportunity to observe in his friends of other faiths.

Stensen was not far from Catholicism. The only change that he perceived in himself was, that he saw less in his earlier religious belief to maintain, and more and more laid aside the resentment which he felt against other faiths. During his journey to Paris in 1664 he met a Jesuit father in Köln who told him many things about Catholicism and asked him questions in regard to his own belief that he found hard to answer. Here again his active mind was directed into new lines of thought. Certain it is that his intercourse with Bossuet in Paris removed many of his prejudices against Catholicism.

You will recall that in 1666 Stensen went from Paris on a journey; this brought him to Rome and later to Livorno just at the time of the Corpus Christi procession, which made a great impression on him. From Livorno he went to Florence and became connected with the Hospital of Santa Maria

Nuova; a Lutheran connected with a Catholic institution, reversing the position which he later occupied: a Catholic connected with a Lutheran institution.

One day Stensen came into the pharmacy connected with the Cloister attached to the hospital. There he met Sister Maria Flavia del Neno who had charge of the pharmacy. She belonged to a prominent family in Tuscany and had been in the Cloister since 1631. Quite naturally, she regretted that the noted anatomist and physician was a Lutheran. The devout nun took this seriously to heart and she sought by prayers and friendly words to win him for the Catholic church. Stensen listened to the unaffected words of the Sister willingly for they came from a heart that, as he soon noted, was concerned for his best welfare.

In Florence, Stensen met still another woman who was to be influential in forming his decision. As body physician to the Grand Duke, and a famous anatomist, he easily gained entrance into the associations and scientific circles of the city. Among these, the most noted, was one that assembled at the house of the ambassador from Lucca, Arnolsini. His wife, Signora Lavinia, was everywhere known as a generous and devout woman. She soon discovered the lofty sentiments of the young Protestant savant and joined with Sister Flavia in prayers and penance that they might win from God his conversion.

As Signora Lavinia saw with what industry her friend studied the Catholic teachings, she urged him to talk with her father-confessor, the Jesuit Savignani. The nun gave him the same advice. Stensen followed it and consulted him; he soon gave him his complete confidence and opened to him his innermost thoughts. They frequently met and held long conversations together. By means of these interviews the last doubts were soon removed. Stensen's mind was convinced, but as yet the last "I will" would not come from his lips. When at last it did come, it formed the sudden conversion spoken of by many authors. On the Feast of the Immaculate Conception, November 2, 1667, Stensen consummated his renunciation before the Nuntius. In Florence great joy prevailed over his conversion.

In December, 1667, Stensen's friend, Viviani, wrote to Magalotti, who was at that time in Flanders, that on the very day that Stensen finally appeared before the Nuntius, after he had declared his conversion, he received a letter from the Danish King offering him the professorship at Copenhagen with a yearly compensation of 400 scudi with the prospect of increased compensation. Stensen did not start at once on his journey for Denmark, but wrote the King asking if he were willing that he should change his belief; but no word came from Denmark. We know that during the following years Stensen wandered through Austria, France and Holland where he remained waiting for an answer to his letter to the King, who was at this time very ill and who died the 2d of February, 1670.

While Stensen was waiting in Holland there arose in Denmark, a man who exercised a great influence on the later

development of the kingdom. This man was Peter Griffenfeld. Under Friedrich III he had been advanced to honorable position and Christian V made him his Prime Minister. Science found in him a friend and supporter. In his inaugural address, Stensen, thanked him for his appointment in the university. Griffenfeld for a long time strove for freedom of religious belief; finally, on the 26th of September, 1671, a royal decree permitted the Catholics to build a church.

On the 13th of February, 1672, Christian V sent an order to Stensen to come to Denmark and stated that he was to have a yearly pension of 400 Reichsthaler and that his pension would begin as soon as he began his homeward journey. Stensen's friends were afraid that he would go back entirely to his scientific work. Magalotti wrote to Falconieri "freedom of thought has robbed us of Stensen"; but such was not the case.

On the 3d of July, 1672, Stensen returned to Copenhagen and took up his residence with his sister. From her house he wrote Sister Flavia at Florence "I am living with my sister. I have perfect freedom; no one says aught against me since many hold the belief that every one is saved in his own religion, if only he lives rightly."

With the return of Stensen to Copenhagen there reappeared the golden days of Pauli and of Bartholin. In his inaugural address Stensen showed himself to be a man of deep religious convictions as well as a true scientist. I will quote a single passage:

What one sees is beautiful; more beautiful what one knows; but by far the most beautiful things are beyond our knowledge. It is the true purpose of anatomy to direct the observer through the astonishing structure of the body to the dignity of the soul, and finally to lead him through the wonders of both to the knowledge and love of the Creator. For who can contemplate the wonderful structure of the human organism without asking who is its author?

The University of Copenhagen was not, however, to retain Stensen for any great length of time. He became involved in a controversy with the rector of the high school at Herlufsholm, Johannes Brunsmann. His position as a Catholic professor in a Lutheran university was an anomalous one and probably the cause of much petty jealousy and religious contention. Just what the cause was we do not know, but on the 26th of May, 1674, he resigned his position and laid aside forever the scalpel and henceforth devoted his energies to the church.

It may be well at this point to consider the contributions which Stensen made to our anatomical knowledge and the position which he occupies in the history of anatomy. Stensen's investigations and anatomical career fall in a time which was rich in discoveries and brilliant investigators. Just as Stensen began his studies Harvey, the discoverer of the circulation, died (1657). The elder Bartholin investigated especially the lymphatics and established the first anatomical museum. Among the friendships which Stensen

formed during his journeys in Holland, France and Italy we find such well known names as Sylvius, van Horne, Swammerdam and Malpighi. Leibnitz and v. Haller ascribe to Stensen a high place in the annals of anatomy. Häser, in his "Geschichte der Medizin" says: "To the most meritorious anatomists of the seventeenth century belongs Niels Steno of Copenhagen, the most illustrious student of Thomas Bartholin. Steno was rightfully considered one of the greatest discoverers of his time; there is no part of the human body the knowledge of which he did not enrich."

He discovered the duct of the parotid gland, of the sublingual gland and of the buccal glands. He also described the lachrymal gland and its duct, thus clearing up a much disputed subject. He had no microscope and knew nothing about capillary circulation, yet he was able to formulate a process of secretion which Foster says, "went very near the truth and served as a useful basis for further inquiry."

He is very clear in differentiating between conglomerate (secreting) and conglobulate (lymphatic) ductless glands. Although he did not properly interpret the mechanics of muscular contraction, he did point out that the action of muscles does not depend upon an increase or loss of their substance. His recognition of the heart as a muscle was, next to the discovery of the circulation by Harvey, the greatest advance in our knowledge of the circulatory apparatus.

I have already spoken of his studies in neurology and their influence on modern investigations of that organ; Stensen also made numerous studies in embryology. But more important than his discoveries in anatomy are the objects and methods of his investigations; he clearly tells us that the advancement of medicine must rest upon an anatomico-pathological foundation. A statement that time has shown to be true.

In looking through the literature for an estimate of Stensen's work in geology, the most concise account I have been able to find is in Zittel's "History of Geology and Palaeontology"; a work of recognized authority written by one of the greatest of the modern paleontologists. In the following paragraphs I have incorporated nearly all of Zittel's statements.

Stensen was one of the most enlightened geologists of the seventeenth century. He begins his work on the earth's crust by comparing fossil teeth found in the deposits of Tuscany with the teeth of living sharks. He then investigates the origin of fossiliferous deposits and compares them with unfossiliferous rocks. The latter, he says, were formed before life existed on the earth, at a time when the earth was enveloped in a universal ocean.

Stensen argued from the traces of salt and the presence of marine animals, and even ship flotsam in certain deposits, that these had been formed on the sea-floor; whereas the presence of a terrestrial fauna and of rushes, grasses and the stems of trees in other deposits, indicated that they had accumulated in fresh water basins. Stensen was the first to

enunciate definite natural laws governing the formation of a stratigraphical succession in the earth's crust.

Stensen also realized that a series of strata originally horizontal might become relatively displaced by subsequent earth movements. He cited examples of local crust-inthrow, showing how individual strata might remain horizontal, while others might be tilted or even thrown into a quite perpendicular position, others again might be bent into the form of arches. The occurrence of crust-inthrows, together with the effects of surface denudation, might give shape to mountains and valleys, plateaus and low lying plains. Mountains, he said, might also originate from the upward action of the volcanic forces on the crust. In cases of active volcanic eruption, ashy and fragmental rock material were ejected, intermixed with sulphurous vapors and mineral pitch.

Thus Stensen's work already contained the kernel of much that has been under constant discussion during the two centuries which have passed since his death. If one reads the most recent text-books of geology, it will be evident that science has not yet securely ascertained the share that is to be assigned to subsidence, to upheaval, to erosion and to volcanic action in the history of the earth's surface conformation in different regions.

Stensen's work "*De solido intra solidum naturaliter contento*," was first published in Florence in 1669, and was intended merely as the prodrome of a larger work: but no later work appeared. A second edition was printed at Leyden in 1679, and a third edition was published in Berlin in 1904 two and a quarter centuries after the first edition appeared. The original edition of Stensen's little book is a bibliographical rarity.

We will now go back to the year 1674. When Stensen left Copenhagen in July of that year, he journeyed leisurely to Florence where he took charge of the education of the son of the Grand Duke Cosimo III. By some it is asserted that this was the occasion of his resignation. Facts do not, however, substantiate this statement.

The conversion of Stensen to Catholicism in no way interfered with his studies. After his conversion he occupied the chair of anatomy at Copenhagen and wrote his epoch-making work on geology, to which I have just referred. That the acceptance of Catholicism did not at that time necessarily kill science in the man is shown in the case of Winslow, Stensen's grand-nephew, who also, after leaving Denmark, became a Catholic and was one of the great anatomists of Paris.

Although Stensen, while at Copenhagen, had full liberty he did not in his lectures permit religion to supersede anatomy. Still he had a far stronger desire to communicate the fruits of his religion to his compatriots than to transmit to them the knowledge of anatomy: the moral appealed to him more than the physical.

In 1675 Stensen became a priest. Just when and where he took holy orders I have been unable to ascertain. On Sunday the 25th of September, 1677, Pope Innocent XI con-

secrated him Bishop of Titipolis. A short time after this, Jean Frederiek, Prince of Braunschweig, who had already abjured Lutheranism called him to his court. Innocent XI consented and bestowed upon him the title of "Apostolic Vicar for the Northern Missions." It was for this reason that Stensen visited the different cities of Germany; Münster, Hannover and Mecklenburg being the principal scenes of his missions.

When Frederiek died suddenly, his brother, Bishop of Osnabruck, succeeded him; and, as he was a Lutheran and a very zealous partisan of his religion, he enjoined upon Stensen to leave his country. Stensen went to Münster; from Münster he went to Hamburg, and, after a short and unsatisfactory stay, to Swerin where he led a quiet and peaceful life and died November 25, 1686, at the age of 48.

The death of Stensen made a sensation among the savants of the world. Men of letters had watched him. His rare knowledge of anatomy and his unexpected conversion to Catholicism made an epoch in the history of science. The Grand Duke of Tuscany hearing of his death desired to have his body. He sent immediately an order to transport it to Florence where he had it entombed with the Grand Dukes in St. Lawrence.

Stensen's zeal for the church and his religion, his lovable character and kind sympathy made him unusually successful in his work. The text chosen for his funeral discourse by Engelbert Schmall, who for five years was Stensen's chaplain, "Follow me, I will make you fishers of men," plainly showed the estimate placed on the life work and the character of the subject of this sketch.

NOTES.

The main facts of this sketch are derived from Plenkers. See Bibliography.

The following variations in the spelling of Stensen's name are met with in the literature: Steno; Stënon; Stenone; Stenonis; Stenonius. In the "*Epistolarum*" of Bartholin and in the "*Acta*" the last two forms are used. The signature of the letters in the *Epistolarum* is "Stenonis". I have followed Plenkers and used Stensen because it is the modern Danish usage and also because Stensen signifies "son of Sten".

An illustration of the "*Domus Anatomica*," and of its amphitheater, in which Stensen gave his lectures may be found in Bartholin's "*Cista Medica Hafniensis*"; Hafniae, 1662; also in Chievitz, "*Anatomiens Historia*"; Copenhagen, 1904. Chievitz gives a number of illustrations of persons and places mentioned in this paper.

Stensen did not take his medical degree at Copenhagen. Where and when he did take it no one knows. Plenkers thinks he received it in 1665 at some University in southern France. Bartholin does not address him in his *Epistolarum* as "Doctor" until 1667.

I have not been able to consult Stensen's original publications. Abstracts and reprints may be found in Vesling's "*Syntagma anatomicum*"; Amstelodami, 1666; and in Mangetus "*Bibliotheca anatomica*," Geneva, 1685. The notes sent by Stensen to Bartholin and the correspondence of Bartholin with Stensen, Ole Borch and Blasius I have read; they are found in the two publications given under Bartholin in the Bibliography. The complete text of Stensen's inaugural address is given in *Acta Hafniensis*, Vol. II.



Nicolaus Stenonis

FIG. 1.—From Plenkers' "Niels Stensen."



FIG. 2.—Thomas Bartholin. From Chievitz "Anatomiens Historie."



GERARDUS BLASIUS
MEDICINÆ DOCTOR, ET PROFESSOR.

FIG. 3.—From Veslings' "Syntagma Anatomicum, Exhibente Blasio."

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A BRIEF HISTORICAL SKETCH OF SOME OF THE EARLY STUDIES OF THE FINER STRUCTURE OF PLANT AND ANIMAL TISSUES.*

By RICHARD M. PEARCE, M. D.,
University of Pennsylvania, Philadelphia.

The theory which is based on the principle that all animal and vegetable structures are composed of cells and that all cells are derived from preexisting cells and which is generally considered to be one of the greatest and most important generalizations in biology—ranking with Darwin's theory of evolution—is usually linked with the names of Schleiden, Schwann and Virchow, representing the period from 1838 to 1858. The work of the three individuals mentioned must, it is true, always stand as the most important determining events in the development of the cell theory, but much of interest to workers in the biological sciences preceded the studies of these three great investigators and many important studies of cell structure followed their announcement and led eventually to the exact knowledge of mitosis which we associate with Flemming's publication in 1882. Of the work and theories before the time of Schleiden we hear little, and the many valuable detailed studies, based on the work of Schwann and Virchow, have been obscured by the establishment, later, of the theory of mitosis. All have a very definite historical value, but it is the earlier work that has, in view of the primitive methods of investigation, a peculiar interest. After Schwann the sequence of discoveries is more or less logical, but the work before Schleiden—the change from the conception of animal tissues as "fibers," "globules" or "molecules" to to the conception of tissues and organs built up through a definite, even mathematical, arrangement of cells is an irregular sequence of hard won advances covering a period of more than 150 years, a story, moreover, of advances coinciding with improvements in the microscope, which correlation adds not a little to the interest of the history of cell studies.

The story begins with the efforts of five individuals—Hooke, Swammerdam, Leeuwenhoek, Malpighi and Grew, who, working contemporaneously, investigated the structure of both animal and vegetable tissues. Swammerdam worked

chiefly with insects, Grew and Malpighi published most complete descriptions of plant structure and Hooke, a free lance, studied whatever was at hand. Previous to their observations, there appears to be little work of any importance. Grew speaks only of the work of Highmore, Sharrock and Hooke as earlier than his own. Of Sharrock I can find no record that he made an important contribution to plant structure; my search of contributions under the name Highmore yields only a description by Nathaniel Highmore¹ of the generation of seeds with some observations on the chick embryo.² It is most convenient, therefore, despite the chance of doing an injustice to Highmore or Sharrock, so conscientiously mentioned by Grew, to begin this account with the year 1671 in which most important contributions to the subject of plant structure were made simultaneously to the Royal Society by Grew and Malpighi. The former refers to this coincidence in his "Anatomy of Plants," published in 1682.³ After stating that he had begun the study of plant structure in 1664 and completed his first study in 1670, he refers to his first book "The Anatomy of Vegetables" and says, "the same day, December 7, 1671, in which my book, then printed, was presented to the Royal Society; there was also presented a manuscript (without figures) from Seignior Malpighi, upon the same subject; dated at Bononia, November 1, 1671, the same which Mr. Oldenburge, when it came to be printed, calleth his idea." The last phrase suggests that the question of priority was as much a cause of trouble then as it has been since. Of "Mr. Oldenburge," however, I can find no record that he made important contributions to this subject previous to those of Grew, Malpighi and Hooke. That Grew appreciated the importance of his observations is evidenced in the wording of his dedication of the book to Charles II. "Your Majesty will find that there are Terrae Incognitae in Philosophy as well as in Geography. And for so much as lies here, it comes to pass, I know not how, even in this inquisitive age, that I

* These notes were collected during the preparation of material for lantern demonstrations, illustrating the development of the various medical sciences, as given, during the past year before the Medical Club of Albany, N. Y., the Sigma Xi Society of the University of Pennsylvania, the Section on the History of Medicine of the College of Physicians of Philadelphia and the American Philosophical Society.

¹ The History of Generation, etc., London, 1651.

² One reads with interest in view of the contemporaneous efforts mentioned above, that Highmore's book is dedicated to Robert Boyle.

³ Grew, Nehemiah: The Anatomy of Plants with an Idea of a Philosophical History of Plants, London, 1682.

am the first who have given a Map of the Country," and again, "In sum, your Majesty will find, that we are come ashore into a New World, whereof we see no end."

Malpighi's letter of transmissal to the Royal Society, shows the importance which he, likewise, ascribed to his investigations.⁴ Grew's numerous plates as also those of Malpighi present figures illustrating the finer details of plant structure. They show, in brief, that plant tissue consists in part of little cell-like cavities and in part of long tube-like vessels. This conception of vegetable tissue is one of small vesicles or bladders clustered together and intermixed with ligneous fiber. Grew, for example, compared cellular tissue to the froth of beer or of beaten eggs. Malpighi showed that the cells could be separated one from another, and gave to these bodies the name "utriculus." It is not to be supposed, however, that they had the conception of cells which we have to-day. Their

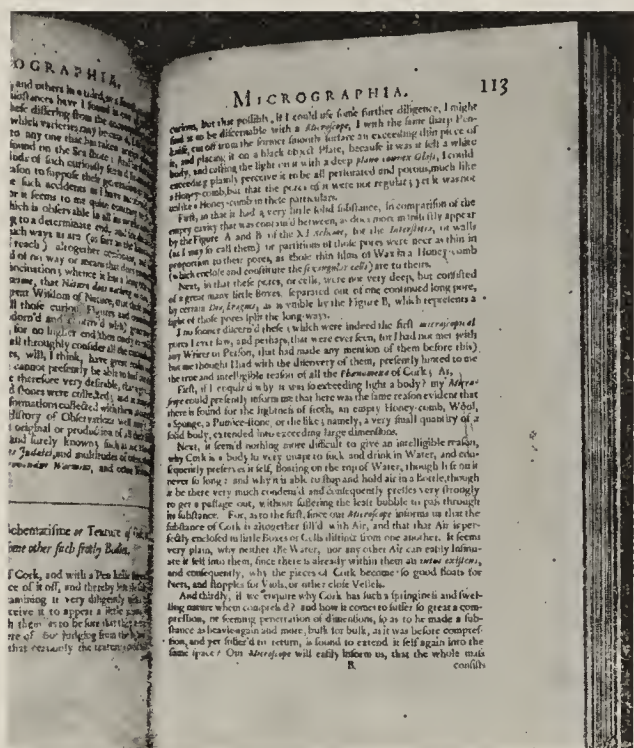


FIG. 1.

conception of a cell was that of a cavity and not of a minute protoplasmic mass. As the Latin "cell" was in its earliest application "a small detached room in a building, particularly a small monastic house"⁵—and was also used to describe a small sleeping apartment, and later a room in a prison, and likewise the small compartments composing a compound structure, as a honeycomb, so it was applied by early microscopists to the spaces which they saw in vegetable or animal tissues. Its first use in this latter sense appears to be by Hooke,⁶ who, in 1665, observed and described the vesicular nature of cork and similar vegetable substances and applied to the cavities the term "cells." (See Figs. 1 and 2). In the same sense the word

"cellula" is used by Swammerdam⁷ in describing the nests with many compartments of various insects.

During this period certain other cells were at least seen and pictured, if not wholly understood or seriously studied. Thus Swammerdam saw the red blood corpuscles and recognized them as such; Malpighi likewise saw them in the mesentery but interpreted them as fat droplets; Leeuwenhoek accurately described and pictured them and at the same time supplemented Malpighi's discovery of the capillaries—the necessary link to the completion of Harvey's theory of the circulation of the blood. A protozoan, a form of vorticella in all probability, was seen by Leeuwenhoek (1675), who also saw and pictured several forms of bacteria. Leeuwenhoek (or his pupil, Ludwig Hamn), also saw spermatozoa (1677). The conception which these early observers had of the structure of cells was not that which we have to-day. Leeuwenhoek, for example, went beyond the limits of simple observation and ascribed to his "spermatic animalecula" a system of muscles, tendons and articulations by which they moved their tails,

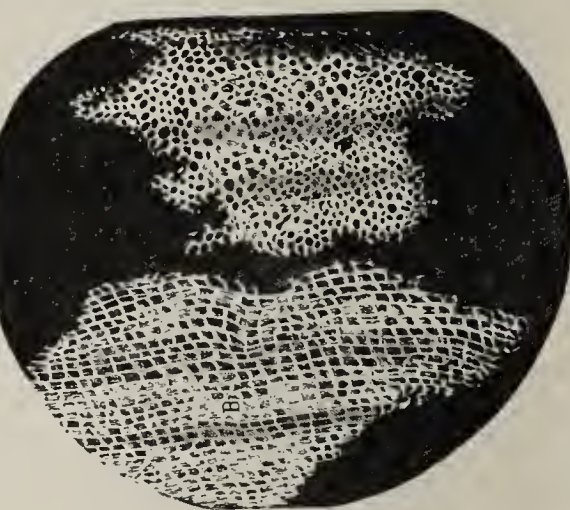


FIG. 2.

and he suggests that the animalcula of stagnant water (protozoa) have organs similar to those of the higher animals.

One cannot avoid being impressed by the industry and detailed observation of these early microscopists, and though often it appears that they sought merely the curious and odd, one examines with amazement the wide scope of their work. Boerhaave's edition of Swammerdam with its parallel columns in Latin and Dutch, and voluminous plates on many forms of insect life, offers glimpses of fundamental observations on the contraction of striated and cardiac muscle and on phenomena of respiration in mammals. One of the most striking plates is that dealing with certain phases of the life history of the mosquito, a species of *Culex* with a figure of the larval form and its breathing apparatus worthy of any modern work, and which could be used as an explanation of the efficacy of the modern oil treatment of breeding pools. Likewise Leeuwenhoek's observations cover a great range, as the animalcula of various fluids, the distribution of the blood capillaries, the

⁷ Johannes Swammerdam: "Biblia Naturæ sive Historia Insectorum"; arranged and published by Boerhaave, 1738-58, after the author's death, but representing work done between 1665 and 1680.

⁴ Anatomie Plantarum; see Opera Omnia, 1687.

⁵ Encyclopedia Britannica.

⁶ Hooke, Robert: "Of the Schematisme and Texture of Cork, and of the Cells and Pores of some other such frothy bodies" beginning on page 112 of his "Micrographia, or some Physiological Description of minute bodies by Magnifying Glasses," London, 1665.

structure of feathers and of insects, and though his microscopes, according to Baker, magnified only 40 to 160 times, he pictured various bacteria. Hooke, though he made many fundamental observations, was interested also in the casual and curious, as the microscopic appearance of an ink drop, the point of a needle, or the edge of a razor.

Grew devoted his efforts almost entirely to vegetable tissues but Malpighi in addition to the study of plants made most important contributions to the finer structure of animal tissues, as of the capillaries, the surface of the tongue and the structure of the skin, spleen and lung.

A word must be said about the microscopes of this period.⁸ There has been much discussion of the earliest use of lenses for purposes of magnification, and of the first use of the compound microscope. The invention of the latter is usually credited to Zacharias Jansen, in 1590; simple lenses appear, however, to have been used since the time of Seneca, who died 65 A. D. At the time of the earlier discoveries in histology, which are here discussed, both simple and compound microscopes were in vogue, the former as made and used by Leeuwenhoek, and the latter by Hooke. Leeuwenhoek's single lens

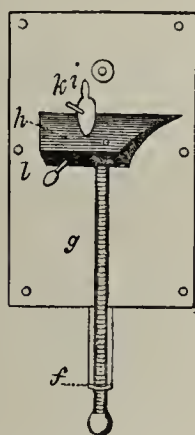


FIG. 3.

was set between two plates of silver perforated with a small hole, with a movable pin before it, upon which to place the object and adjust it to the eye of the beholder, (see Fig. 3). His use of this instrument corresponds presumably to a period shortly before the year 1675 in which his first contribution appears in the *Philosophical Transactions*. It has been said by many authors that Leeuwenhoek used globules or spheres of glass, such as had been used by Hooke, but this is not the case, for in the cabinet of twenty-six microscopes left by Leeuwenhoek, at his death, to the Royal Society, each has a double convex lens and not a sphere or globule (Baker, 1740).

The amount of labor entailed in Leeuwenhoek's microscopic studies may be appreciated, from the fact that each microscope was prepared for one or two objects only and could be applied to no other. He is said to have made some hundreds of these microscopes, the entire manufacture, including the grinding of the lenses, being the work of his own hands. The highest

⁸ The summary here presented is compiled from Adams, George: *Micrographia Illustrata*, London, 1747; Quekett, John A.: *Practical Treatise on the Use of the Microscope*, London, 1848; and Hogg, Jabez: *The Microscope: its History, Construction, and Application*, London, 1859.

magnifying power of his lenses was 160 diameters and the lowest 40.

Hooke's microscope, which he described in 1667 at the time of the publication of his "*Micrographia*" was a compound instrument with ocular, objective and a middle lens arranged in a tube much like that of the modern microscope. He appears to have been the first to invent a method of illuminating opaque objects, this being the now familiar use of a glass globe filled with brine placed immediately in front of the lamp. The pencil of rays from the globe was received by a plano-convex lens, placed just above the object holder and with its convex surface toward the globe. The object holder was a simple upright with an adjustable cross-pin.

Hooke also made globular lenses by melting in a flame fine threads of glass until the glass ran into globular form; the end where the thread was broken off was afterwards ground and polished. For these he claimed greater magnification than for "any of the microscopes."

In 1698, Bonanni invented a compound microscope, to be used in a horizontal position, with coarse and fine adjustment; the former was obtained by a rack and pinion moving the entire frame, the latter by a screw in the end of the compound

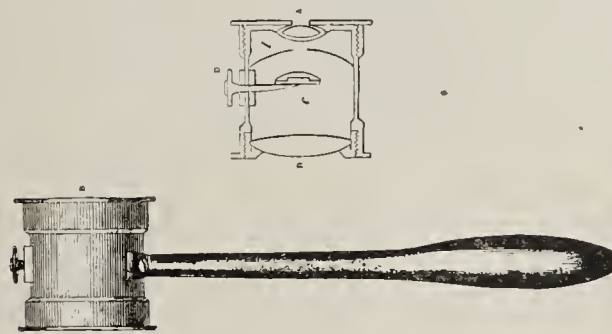


FIG. 4.

near the objective. He also used a short tube in which were two double convex lenses to condense the light upon the object, and an object holder placed between the objective and the source of illumination. After Bonanni, few important improvements, with the exception of Newton's introduction of mirrors, first in the reflecting telescope and then the reflecting compound microscope (1672), were made for many years. The study of tissues continued, however, but for the most part as a matter of curiosity rather than of scientific interest.

Later, a few individuals made most important contributions to the study of structural details. Lieberkuhn, in 1738, developed the so-called solar microscope, with its concave silver speculum, for the viewing of opaque objects. With this he made most important studies of the minute structure of the mucous membranes of the alimentary canal. He⁹ used it also in connection with the injection of the mesentery and other minute tissues in the study of the circulation of the blood and chyle. The plan of his microscope is as follows (see Fig. 4): The sun's rays fall on a condensing lens (B)

⁹ Joannis Nathaniel Lieberkuhn: See, "*Dissertationes Quator*," (1) valve of colon and the vermiform appendix, (2) villi of intestine, (3) methods of studying structure of organs and (4) description of a microscope. Collected and published by J. Sheldon, London, 1782. The first and third of these appeared originally in 1739 and 1748, respectively.

placed at one end of a brass tube about one inch long, and one inch in diameter; the light from this lens is concentrated on the speculum (1) which again further condenses the rays on the object on the disk (C), which object, when so illuminated, can be readily adjusted by the little knob (D) so as to be in the focus of magnifying lens (A). Lieberkuhn worked chiefly with minute injected specimens and these, when placed on the object holder, were covered with a varnish. As was the case with Lceuwenhoek, the microscope went with the preparation to be studied, and according to Quekett, the Museum of the Royal College of Surgeons contained in 1848 twelve such exhibits which, after a century, were unchanged except for slight cracks in the varnish over the mounted specimens.

These various advances in the making of microscopes had

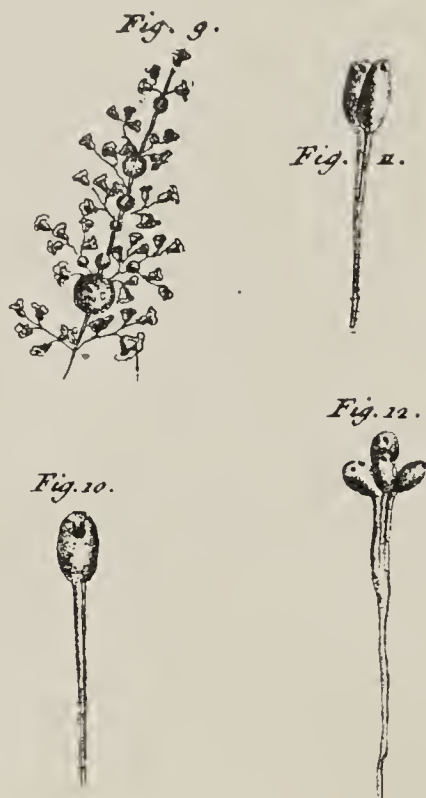


FIG. 5.

a direct bearing on the development of the cell theory in that they encouraged the study of the finer structure of plant and animal tissues. The conception of the essential structure of these tissues was, however, no more exact than in the time of Grew and Malpighi. Nevertheless, noteworthy discoveries, though not always understood, were made. Thus many forms of protozoa were studied and described, and finally Trembly¹⁰ (1744-1747) studied the life history and observed the longitudinal division of a fresh water protozoon (see Fig. 5). In 1770, Hill published a detailed account of the microscopic structure of timber. Each of these publications revived at the time the pursuit of microscopic studies, as did also the invention by Adams,¹¹ somewhat later, of a machine for cutting

¹⁰ Trembly, Abraham: Observations upon several newly discovered species of fresh water polypi. Philos. Trans. Royal Society, 1756, XI, Part III, 801, 807. (Read Nov. 22, 1744, and May 21 and June 18, 1747.)

¹¹ Adams, G.: Essays on the Microscope, London, 1798.

transverse sections of wood so that they might readily be examined by the microscope. That there was also at this time a popular interest in the use of the microscope is shown by the titles under which Baker's¹² books appeared.

It was not, however, until 1806 that a fundamental discovery, capable of advancing the knowledge of tissue structure beyond the conceptions of Grew, Malpighi and Hooke, was made. Adams in 1798, in discussing the structure of plants, makes the statement concerning cellular tissue that "the nature of this substance, its form and structure are at present little known," and quotes chiefly Grew and Malpighi, but mentions also Duhamel, Hill, Bonnet and DeSaussure. A great advance was, however, made when Treviranus,¹³ as a result of the study of the growing parts of young plants, discovered that the tubes and vessels of Malpighi *arose from cells* by becoming elongated and attached end to end, the intervening walls eventually breaking down. Although this discovery is credited to Treviranus there seems to be some question as to whether he thoroughly understood that the vessels were modifications of cells, for we find von Mohl¹⁴ in 1852 stating that early errors "were followed even by Treviranus" and "I was the first to detect their origin from rows of closed cells." von Mohl made many important contributions to the subject of plant structure. He began his work in 1828 with an investigation "On the Pores of Cellular Tissue," was appointed Professor of Botany at Tübingen in 1832 and made many contributions to the study of vegetable cells,¹⁵ and as we shall see his work was an important factor in setting aside some of Schleiden's erroneous conclusions. This work by the early botanists gave to the cell some importance, but no law was established until the time of Schleiden and of Schwann, and though many interesting observations were made, the significance of these was not always appreciated. This is especially true of the first description of the nucleus presented by Robert Brown¹⁶ in 1831, as an incidental result of his study of the organs and mode of fecundation in orchids. Brown's account is purely descriptive, with no attempt at explanation or theory, but in view of the important position which the nucleus now occupies in cytological problems, some of his sentences are worthy of quotation. "In each cell of the epidermis of a great part of this family (Orchideae) especially of those with membranous leaves, a single circular areola, generally somewhat more opaque than the membrane of the cell is observable"; and again, "This areola, or nucleus of the cell as

¹² Baker, Henry: The Microscope Made Easy, London, 1754; *ibid.*, Employment for the Microscope, London, 1764.

¹³ Treviranus, C. L.: Von inwendigen Bau der Gewächse, 1806. This work I have been unable to examine in the original, as it is not catalogued in the most important libraries of this country.

¹⁴ English Translation. Principles of the Anatomy and Physiology of the Vegetable Cells, London, 1852.

¹⁵ See Vermischte Schriften botanischen Inhalts von Hugo von Mohl, 1845; and English translation of "de Palmarum Structura" in Reports and Papers on Botany (Ray Society), London, 1849.

¹⁶ Brown, R.: On the Organs and the Mode of Fecundation in Orchideae and Asclepiadae, Transactions of the Linnæan Society, 1833, XVI, 685 (read at meetings of Nov. 1 and 5, 1831).

perhaps it might be termed, is not confined to the epidermis, being found . . . in many cases in the parenchyma or internal cells of the tissue."

This is the first description of the nucleus and the first observation of its occurrence in all cells. It had undoubtedly been seen before, for Brown in the same communication refers to the drawings of Meyen, Purkinjé, Brongniart and Bauer in which are depicted the epidermis and the structure of leaves, and which offer a few indications of structures corresponding to the nucleus, or areola, but, as Brown goes on to say, so little importance was usually attached to this areola, that it is seldom mentioned in the text. It remained for Brown to describe the structure and to give to it a name.

These advances, beginning with Treviranus corresponded to a new interest in the improvement of the microscope. Serious attempts to discover a perfect achromatic compound microscope began about 1800, and although it was not until about 1830, largely as the result of the experimental work of Joseph Jackson Lister (the father of Lord Lister), that exact knowledge of the proper combination of lenses and the use of a transparent cement (Canada balsam) for the fixation of the same was obtained, still, the improvements were such as to aid the work in histology.

As Schleiden's work appeared in 1838 and Schwann's in 1839, and especially as Schwann acknowledges that he received the stimulus for his work from a conversation with Schleiden, the conceptions of these two founders of the cell theory may be considered at one and the same time. In this connection it is worth while also to recall that these two, as likewise Virchow, who later had so much to do with the development of the cell theory, were pupils of Johannes Müller, who, before Schleiden's announcement, had published observations on the vegetable cells, and before Schwann, had emphasized the similarity¹⁷ in structure between vegetable cells and certain embryonic animal tissues, as the chorda dorsalis. It was Schleiden,¹⁸ however, who definitely established the fact, as the result of his work on the Phanerogamia, that all vegetable tissues are composed of cells each of which contains a cystoblast (nucleus) and that in the undifferentiated parts of the young plant these nuclei are the earliest demonstrable bodies and that it is about such nuclei that the cell protoplasm accumulates.

Schleiden's description of the development of cells in vegetable tissue reminded Schwann of similar pictures he had seen in the embryonic tissues of animals and upon his work with the chorda dorsalis and young cartilage was based his account of the accordance in structure of animal and plant tissue.¹⁹

¹⁷ Purkinjé and Valentine are also credited with calling attention to the similarity of vegetable and animal tissues. See Tyson, J.: *The Cell Doctrine*, Philadelphia, 1878.

¹⁸ Schleiden, Matthias Jakob: *Beiträge zur Phytogenesis*, Müller's Arch., 1838, page 137; also English Translation, Sydenham Society, 1847.

¹⁹ Schwann, Theodor: *Microscopische Untersuchungen über die Uebereinstimmung in der Struktur und dem Wachsthum der Thiere und Pflanzen*, Berlin, 1839; also English Translation, Sydenham Society, 1847.

In these embryonic tissues he found the development of cyto-blasts with their granules (nucleoli) as described by Schleiden and later the development of the cell protoplasm about the nucleus. Thus Schwann demonstrated for animal tissues what Schleiden had shown was true for vegetable tissues, that tissues were made up of cells which develop at an early embryonic period from nuclei in an undifferentiated matrix. Schwann's work, therefore, was of the utmost importance in that he established the principle of the origin of all tissues from cells. Schwann studied many types of tissue including many highly differentiated as the nails, the teeth, and feathers, and showed that no matter how tissues varied in structure, no matter how simple or how complicated they might be, all were composed of cells more or less modified to serve the peculiar function of the tissue in question. This work led to his conclusion. "We have seen that all organized bodies are composed of essentially similar parts, namely, of cells; that these cells are formed and grow in accordance with essentially similar laws; and, therefore, that these processes must in every instance be produced by the same powers."

Certain views of Schleiden and Schwann were, as knowledge of the cell increased, abandoned, but their conception of all tissues as composed of cells was the incentive to the detailed investigations which followed. The view that cells arose from a homogeneous cytoblastema or matrix, by a process analogous to crystallization, gave way to the knowledge that all cells are derived from preexisting cells as expressed in Virchow's aphorism *omnis cellula e cellula*, and also the views as to the importance of the cell wall and of the cell cavity gave way later to the knowledge that the nucleus is the essentially important part of the cell.

It is not surprising, however, when we consider that the question of cell division was not settled until 1882, that all was not made clear at once. Many views, as von Mohl's theory of the division of vegetable cells by fission, Henle's theory of budding and Schwann's hesitating account of the formation of new animal cells by partition of old ones, did good service in attaching many investigators to the field of cell study. The importance of Schleiden's generalization of the nucleated cell as the fundamental feature of organic structure is fully realized only when one contrasts it with previous views, as the purely hypothetical "fiber" and "organized concrete" theory of Haller (1757), Wolff's (1759) theory of "globules," Oken's (1808) theory of "vesicles" and those of the period immediately preceding Schleiden and Schwann in which were used the terms "molecular granule" and "formation globules," and which were grouped under the general head of the "globular theory."²⁰ It is evident, from these terms, vesicle and globule, that the cell had been constantly seen in all microscopic work and had been recognized as constantly occurring in animal and vegetable tissues, but its significance was not apparent until the generalization of Schwann gave to the cell its proper place in the scheme of animal and plant structure.

²⁰ See Tyson, J.: *The Cell Theory*, Philadelphia, 1878.

After Schwann, the next important studies were those concerning the division of the cell and the importance of the nucleus in this process. Although both Schleiden and Schwann had shown that the new cells developed about the nuclei of the "cytoblastema," the importance of the nucleus in cell formation was not immediately appreciated. That cells divide was cautiously surmised by Schwann, was more boldly stated by Henle (1841), who, however, found no example of it in animal cells, and was supported by Reichert (1840) in his study of segmentation of the egg. (See Figs. 6 and 7 for views concerning cell division in 1855 and 1859.)

The first recognition of the fact that the nucleus shares in cell division is usually credited to Martin Barry (1840), who was supported shortly by John Goodsir (1845) and Remak (1852).

In 1858, however, the cell doctrine was definitely and finally established by Virchow,²¹ who postulated that all biological doctrines, whether dealing with normal or pathological processes, must be based on the fact that all cells are derived from preexisting cells and that the primary origin of all cells is the ovum, thus substituting for Harvey's aphorism *omne*

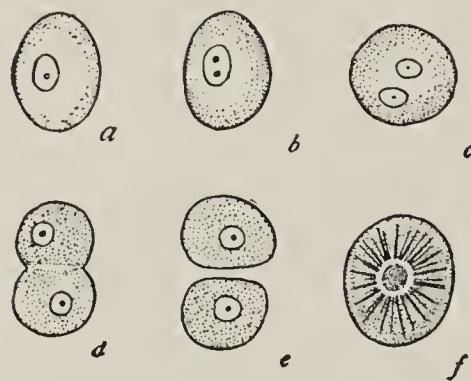


FIG. 6.

vivum ex ovo his own *omnis cellula e cellula*. Virchow stated this as follows: "Where a cell arises, there a cell must have previously existed (*omnis cellula e cellula*), just as an animal can spring only from an animal, a plant only from a plant. In this manner, although there are still a few spots in the body, where absolute demonstration has not yet been afforded, the principle is nevertheless established, that in the whole series of living things, whether they be entire plant or animal organisms, or essential constituents of the same, an eternal law of *continuous* development prevails."

While this announcement had the special effect of giving to pathology a "cellular theory" to replace the older humoral theory, its broader effect was to stimulate the study of the normal cell.

It was evident that the cell must be more thoroughly studied and it is from the period (1860) shortly after this announcement of Virchow, that we date the consistent and and thorough study of that form of cell division now known as mitosis or karyokinesis. We may leave this—the problem

of the nucleus—a moment, however, to say a few words about the cell protoplasm.

About the time of Schleiden and Schwann's work the protozoa, largely as the result of the work of Dujardin²² (1841), were recognized to be simple, slightly differentiated structures, quite unlike the complex organisms described by Leeuwenhoek and his followers, and to be composed of a fundamental living substance to which Dujardin gave the name *sarcodé*.

It was also about this time (1838) that Ehrenberg made his celebrated classification of protozoa, which was so accurate in the description of species that 45 years later Bütschli was able to recognize more than 100 as identical with the well-studied species of his own time.

Likewise at this time (1839) the suggestion was made for the first time, by Meyen, that protozoa might be single cells, the entire infusorian body being analogous to a single plant cell. This theory was applied directly by Barry, in 1845,²³ who also compared the nucleus of protozoa to the cell nucleus

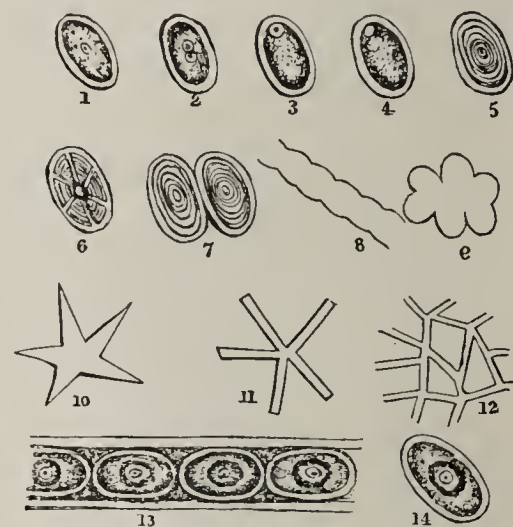


FIG. 7.

of higher animal forms. Finally Siebold, in 1848, asserted the unicellular nature of all protozoa.²⁴

Kölliker, in 1841, showed that spermatozoa are not parasitic animaleules, but not till 1865 was it known that they are complete cells with nucleus and protoplasm.

In accord with Dujardin's conception of sarcodé as the basic substance of protozoa, von Mohl, in 1846, substituted for Schleiden's "plant slime" the term "protoplasm,"²⁵ which had also been used previously by Purkinjé, for the formative substance of young animal embryos. Later (1852) Remak applied the term to the substance of any animal cell. Studies of the streaming of protoplasm within the cell, of ameboid

²² See Dujardin, F.: *Histoire Naturelle des Zoophytes-Infusories*, Paris, 1841.

²³ For the state of microscopic study at this time see Dujardin, F.: *Nouveau Manuel Complet de l'Observation du Microscope*, Paris, 1843.

²⁴ Calkins, G. N.: *The Protozoa*. New York, 1901.

²⁵ For an excellent historical summary of the development of the knowledge of cell structure which is here quoted, see article on "Cytology," by G. C. Chubb, in the eleventh edition of the *Encyclopedia Britannica*.

²¹ Virchow, R.: *Die Cellularpathologie in ihrer Begründung auf physiologische und pathologische Gewebelehre*, Berlin, 1858; also English Translation by Frank Chance, London, 1860.

motion, and also the recognition of cells without membrane, led to the view, now held, that not the cell wall but the nucleus and protoplasm are the essential parts of the cell. This change of view was due particularly to Max Schultze, who showed by his careful comparative studies that one and the same substance—protoplasm—occurred in both the unicellular and the higher forms of plants and animals alike, and while in some tissues, especially vegetable, this substance was as a rule enclosed within a membrane, in many higher animals and unicellular forms a membrane was frequently absent. This constituted, in contradistinction to the "cell theory" of Schleiden and Schwann, his "protoplasmic theory" which defined a cell as "a small mass of protoplasm endowed with the attributes of life" (1861). In the same year Brücke put forth his views of the cell as an "elementary organism" with the assumption that the protoplasm had a complex structure, invisible only because of imperfect methods of observation.

At the same time rapid progress was made (1860-1880) in the knowledge of the nucleus and its part in cell division. Schleiden's "cytoblastema" theory (1838) which postulated the origin of vegetable cells from the fluid of the mother cell by a process analogous to crystallization, the nucleolus appearing first, then the nucleus and finally the cell body—a theory which was extended by Schwann (1839) to include animal cells—did not long remain unchallenged. By 1846, largely as the result of the work of von Mohl and Naegeli,²⁶ botanists recognized the general law that cells arise only by the division of preexisting cells. The application of the law to animal tissues came slowly, but as the result of the work largely of Kölliker, Reichert and Remak, it was possible, as we have seen, for Virchow to make, in 1858, his celebrated generalization concerning the genetic continuity of cells.²⁷

²⁶ See English translation of Naegeli's paper in Ray Society's publication, Reports and Papers on Botany, London, 1849.

²⁷ For a general review of the cell theory in 1853, see Huxley, T. H. The Cell Theory, British and Foreign Medico-Chirurgical Review,

The details of the process of cell division and the importance of the nuclear changes in this process were, however, not worked out for many years; but this period, beginning with the observations of Anton Schneider in 1873 and ending with the publication of W. Flemming's exhaustive studies in 1882, and including the names of many worthy investigators, allowed Flemming to alter Virchow's aphorism to read—*omnis nucleus e nucleo*.

Thus, from Hooke's first use (1665) of the term "cell" to the establishment of the true method of cell division (1882), a period of nearly two and a quarter centuries was required to lay securely the foundations of modern cytology.

ILLUSTRATIONS.

FIG. 1.—Page from Robert Hooke's "Micrographia" (1665). The first description of the spaces in vegetable tissue, from which dates the use of the word "cell" in the histological sense.

FIG. 2.—Robert Hooke's reproduction of the spaces (cells) in cork.

FIG. 3.—Leeuwenhoek's Microscope (1675). A single lens fixed between perforations in two plates of metal. Letter indicate object holder and method of focusing.

FIG. 4.—Lieberkuhn's Microscope (1738). See text for description of structure and method of use.

FIG. 5.—First recorded observation of the method of division of a protozoon (Vorticella). Trembly, 1744-47.

FIG. 6.—Cell division according to Remak (1855). Direct division of blood cells in the embryo chick.

FIG. 7.—Conception of development of animal cells in 1859. Taken from Hogg, The Microscope, London, 1859. 1, Shows a newly formed cell. 2, Subdivision of the nucleus. 3, The nucleus changes its situation, and at 4, subdivides and disappears. 5, The walls of the cell increase in thickness. 6, The cell becomes branched, or stellate. 7, Two cells are seen to coalesce. 8, They have coalesced and run into each other. 9, Again they take another form and become multilocular. 10, 11, 12, Cells sprouting out to form membrane and vessels. 14, Development of complicated cells, which at 13, have coalesced to form tissue.

1853, XII, 282; for the same see Tyson, J.: The Cell Theory, Philadelphia, 1878; the views before and after Virchow's announcement may thus be contrasted.

EARLY HISTORY OF THE CARE AND TREATMENT OF CRIPPLES.

By DOUGLAS C. McMURTRIE, New York.

The cripple has long been considered, at least in literary fields, as the prototype of the handicapped and miserable creature. We may, therefore, expect a study of the history of the attitude of society toward the deformed to throw considerable light on the growth of a sense of community responsibility for the welfare of unfortunate members. The subject thus touches intimately the general history of medicine.

From the earliest times the lot of the cripple has been a hard one. The first mention of physical deformity carries with it stigma in other respects as well. With primitive peoples the cripple was very commonly exposed or abandoned to perish of neglect.¹ Among Indian peoples the Chiriguana

¹ Albert Hermann Post, *Grundriss der ethnologischen Jurisprudenz*. Oldenburg and Leipzig, 1894. Vol. 2, p. 10-12.

are reported as addicted to this practice.² Waitz reports that the Salivas, like many others, are accustomed to destroy deformed children, since they attribute the deformity to the influence of evil spirits.³ The same practice existed among the Carib tribes of the Antilles.⁴ Among the Aztecs⁵ deformed persons could be sacrificed in time of famine and need. They

² Thouar, *Deutsche geogr. Blätter*, vii, 66.

³ Theodor Waitz, *Anthropologie der Naturvölker*. Leipzig, 1892, Vol. 3, p. 394. Also see A. O. Humboldt and Bonpland, *Reise in die Aequinoctialgegenden des Neuen Continents in den Jahren 1799-1804*. Stuttgart and Tübingen, 1845.

⁴ Albert Hermann Post, *Bausteine für eine allgemeine Rechtswissenschaft auf vergleichend-ethnologischer Basis*. Oldenburg, 1880-1881, Vol. 2, p. 119.

⁵ Joseph Kohler, *Recht der Azteken*, p. 46.

could also be sacrificed at the death of kings and great men. Deformed infants were abandoned or killed by various tribes living on the islands of the Pacific; Australia,⁶ Hawaii,⁷ and others,⁸ as they were by some negro-peoples as well.⁹ In the kingdom of Assinie, on the Gold Coast, children with six fingers on either or both hands were buried alive.¹⁰ Among the Indo-Germanic peoples exposure of deformed infants¹¹ was a custom of frequent occurrence. In the early law of Northern Germany the right to kill monsters and deformed persons is often mentioned.¹²

Isolated cases of the practice of the exposure of infants occur in Japan¹³ as in other countries, but it has never approached recognition as a general custom. From the myth of the god Hiruko (leech-child) it may be inferred that the abandonment of deformed infants was not uncommon in the earliest times. The *Nihongi* tells us that the god had completed his third year and was still unable to walk. His parents, therefore, placed him in the rock-camphor-boat of heaven and set him adrift.

Data concerning the exposure of infants in Persia¹⁴ are scanty. According to the Avesta,¹⁵ all deformities were regarded as the work of the Evil One. It is not impossible, therefore, that deformed children were exposed with more or less frequency.

Among the Pima Indians, a North American tribe, with the consent of the parents, deformed infants were taken by the midwife, who watched them until they died of exposure and want of nourishment.¹⁶ So strong was the feeling of the Pimas against the abnormal that they tried in recent years to kill a grown man who had six toes.

In this connection James Mooney, of the Bureau of American Ethnology, in a communication to me, notes as follows:

Among the Kiowa I knew personally a twelve-year-old girl, of receding forehead and halfwitted, who had been buried alive immediately after birth and rescued and brought to the Catholic mission by a captive woman who knew what was about to be done. The missionary priest, from his experience waiting on their sick in camp, believed that they had killed other defective infants

⁶ Albert Hermann Post. *Bausteine für eine allgemeine Rechtswissenschaft auf vergleichend-ethnologischer Basis*. Oldenburg, 1880-1881. Vol. 2, p. 119. Also Joseph Kohler, in *Zeitschrift für vgl. Rechtswissenschaft*, vii, 355. Also Waitz-Gerland, *Anthropologie*, Vol. 6, p. 779.

⁷ Waitz-Gerland, *Anthropologie*, Vol. 6, p. 139-140.

⁸ Albert Hermann Post. *Bausteine für eine allgemeine Rechtswissenschaft auf vergleichend-ethnologischer Basis*. Oldenburg, 1880-1881, Vol. 2, p. 119.

⁹ Albert Hermann Post, *Afrikanische Jurisprudenz*, Oldenburg, 1887, Vol. 1, p. 285.

¹⁰ *Globus*, 1891, No. 11, p. 176, after Reichenbach, *Étude sur le Royaume d'Assinie*. *Bull. Soc. Géogr.* 1890, p. 316.

¹¹ Grim, *Rechtsaltert*, p. 456.

¹² Maurer. *Wasserweihe des germ. Heidentums*, 1880, p. 14 ff.

¹³ James Hastings, *Encyclopædia of Religion and Ethics*, Edinburgh, 1908. Vol. 1, p. 7. Article by W. G. Aston.

¹⁴ *Ibid.*, Vol. 1, p. 7, article by Louis H. Gray.

¹⁵ Vendidad, ii, 29.

¹⁶ Frank Russell, *The Pima Indians*. *26th Annual Report. Bureau of American Ethnology*. Washington, 1908, p. 185.

at birth. I know also of instances of abandonment of the helpless aged in the same tribe.

Travelers have asserted the existence of the practice of killing defective infants, in various tribes, and I am inclined to think that it was quite general. Some tribes, especially in Oregon, kill one of a pair of twins. The reason in both cases seems to have been partly economic, to be rid of a future burden, and partly from a superstitious fear of the abnormal.

With the dawn of our present civilization the condition of the cripple did not improve to as great an extent as we should ordinarily expect. Oriental peoples turned forth their cripples to wander in the wilderness. The inhabitants of Ancient India cast them into the Ganges; the Spartans¹⁷ hurled them from a precipice into an abyss, *Apothelos*. The Jews in the earliest times banished their cripples so that they had, perforce, to beg by the roadsides. The general attitude was to regard physical deformity as a blight sent by God or as a punishment for sin.

The Hebrew Scriptures reflect the attitude that the deformed person must be spiritually and mentally unfit as well. In Leviticus¹⁸ we encounter a passage illustrative of this:

And the Lord spake unto Moses, saying: speak unto Aaron, saying, whosoever he be of thy seed in their generations that hath any blemish, let him not approach to offer the bread of his God.

For whatsoever man he be that hath a blemish, he shall not approach; a blind man or a lame, or he that hath a flat nose or anything superfluous.

Or a man that is brokenfooted, or brokenhanded,

Or a crookbackt, or a dwarf, or that hath a blemish in his eye, or be scurvy, or scabbed, or hath his stones broken;

No man that hath a blemish of the seed of Aaron the priest shall come nigh to offer the offerings of the Lord made by fire; he hath a blemish; he shall not come nigh to offer the bread of his God.

Later on in the same passage it is stated that the reason for this is that the sanctuaries be not profaned.

There are references to the cripple in the Old Testament in the form of similes showing that physical deformity was familiar to the people.¹⁹ The first reference to a deformity caused by accident occurs in the Second Book of Samuel.

And Jonathan, Saul's son, had a son that was lame of his feet. He was five years old when the tidings came of Saul and Jonathan out of Jezreel, and his nurse took him up, and fled; and it came to pass, as she made haste to flee, that he fell and became lame. And his name was Mephibosheth.²⁰

This accident was probably the forerunner of many subsequent accidents to children in charge of nurses.

Kindly references to the cripple in early times are scarce. In Job's recital²¹ of his circumstances when God was with him, recounting his various benevolences, he says, "I was eyes to the blind and feet was I to the lame."

In referring to inheritance, the Dâdistân-î-Dînîk,²² one of

¹⁷ Douglas C. McMurtrie. *The Primary Education of Crippled Children*, New York, 1910, p. 5.

¹⁸ *Leviticus*, xxi, 16-21.

¹⁹ See *Proverbs*, xxvi, 7.

²⁰ *II Samuel*, iv, 4.

²¹ *Job*, xxix, 15.

²² Chapter lxii, paragraph 3.

the sacred books of the East,²³ says, "... and the share of one of the sons, or even the wife of a son who is blind in both eyes, or crippled in both feet, or maimed in both his hands, is twice as much as that of one who is sound."

The Greeks, worshipping as they did the perfection of bodily form, regarded a cripple as the incarnation of everything unlovely,²⁴ not only physically, but also mentally and morally. Homer describes Thersites as possessed of every ugly attribute and equally deformed in body and mind.²⁵ Such was the propensity of this crippled soldier of the army before Troy for indulging in vituperative language that he did not abstain from directing it even against Agamemnon himself. It is related that he ultimately perished at the hand of Achilles, while he was ridiculing the sorrow of that hero for the slain Penthesilia.

The advent of Christianity struck a new note in the attitude toward the crippled and deformed. Even in Isaiah's prophecy²⁶ of the coming Messianic kingdom, he foretells that "then shall the lame man leap as a hart." Christ, referring to His ministry,²⁷ says: "the blind receive their sight, and the lame walk. . . ." It is also related²⁸ that "the blind and the lame came to Him in the temple and He healed them."

Many cures of cripples are also attributed to the Apostles. "A certain man lame from his mother's womb" was healed by Peter.²⁹ It is related that "immediately his feet and ankle bones received strength." During the ministry of Philip³⁰ "many taken with palsies and that were lame, were healed."

During the mission of the Apostle Paul in Lycaonia, he healed³¹ a cripple described as follows: "And there sat a certain man at Lystra, impotent in his feet, being a cripple from his mother's womb, who never had walked." It is interesting to note that this is the first use in the Scriptures of the generic term, cripple. The Greek word *χολός* is used in the original.

The influence of the Christian attitude had some influence upon the lot of the cripple. I recall one illustrative quotation.³²

Also cripples and the sick who remained alive were left to themselves³³ in Iran as in Armenia and they led a wretched existence. In Armenia it was one of the great services of Christianity that it ameliorated the fate of these unfortunates.³⁴

But the new influence was not profound and it did not even

permeate the Church in its later development. During the Middle Ages, those burdened with physical deformity were considered as targets for contempt and ridicule, and contumely was continually heaped upon them.³⁵

The early Romans had the right to destroy a deformed child provided the child were shown to five neighbors and their assent secured. In the Twelve Tables the decemvirs extended the authority of the father so that he, individually, could destroy or remove crippled children immediately after birth. In many instances they were cast into the street or drowned in the lake into which emptied the sewers of the Eternal City. They were exposed in deserts, in the woods on the banks of the Tiber, in the vegetable market, at a certain pillar in the eleventh district of the city, and ironically enough in the very vicinity of the Temple of Mercy. Some few of these unhappy children did not die of exposure or hunger and escaped being torn to pieces by dogs or being eaten by swine. But in spite of their lives being saved, their existence became a wretched and miserable one. They became the slaves of the person who took them up and succored them, and they were intentionally crippled to a greater extent if their deformities when they grew older were not conspicuous enough to render them successful in begging alms for their master's profit. Seneca relates how these unfortunates wandered about exhibiting their mutilated members. He goes on to state that they were intentionally deformed by cutting off their arms, by twisting their shoulders so that they became humpbacked. If the master counts over the daily collection of the beggars and the sum is not enough, he rebukes the wretches, saying: "You have brought in too little, bring hither the whip; you can weep and lament now. If you had appealed this way to the passer-by you would have had more alms and could have given me more." It may be remarked that this system of peonage in mendicancy is in use even to-day in some communities, notably in Italy and Russia. In the former country many children are mutilated so that they may solicit alms in the streets. In Russia a similar practice is indulged in, the cripples being exhibited particularly at ceremonies and processions.

Among the Romans the trade in slave dwarfs became so extensive and profitable that merchants took children and put them in artificial bandages.³⁶ This method instead of making them well-proportioned dwarfs made them misshapen and miserable men. This gruesome torture and unnatural art of making dwarfs is also mentioned by Cardanus.³⁷ *Nascuntur ex parvo patre et matre, fasciis arcte colligantur non affatim nutriuntur, sed teniuntur*, which might be translated: born of small parents, they are laced with bandages and fed, not heartily, but sparely. Dwarfs were utilized by the Emperor Domitian to engage in show battles with women.³⁸

³⁵ Douglas C. McMurtrie, *The Primary Education of Crippled Children*, New York, 1910, p. 6-7.

³⁶ Sigaud de la Fond. *Wunder der Natur*. Part 2, p. 495, also K. F. Flögel, *Geschichte der Hofnarren*, Leignitz and Leipzig, 1789, p. 507-508.

³⁷ Cardanus, *De Subtilit.* Book XI, p. 460.

³⁸ Xiphilinus, *In Domitiano*.

²³ *Sacred Books of the East*, edited by F. Max Müller, Oxford, 1882. *Pahlavi Texts*, translated by E. W. West.

²⁴ Douglas C. McMurtrie, *The Primary Education of Crippled Children*, New York, 1910, pp. 5-6.

²⁵ Homer, *Iliad*, ii, 212 ff.

²⁶ *Isaiah*, xxxv, 6.

²⁷ *Matthew*, xi, 5. Also referred to in *Luke*, vii, 22.

²⁸ *Matthew*, xxi, 14.

²⁹ *Acts of the Apostles*, iii, 2.

³⁰ *Acts of the Apostles*, viii, 7.

³¹ *Acts of the Apostles*, xiv, 8.

³² Fr. Spiegel, *Eranische Alterthumskunde*, Leipzig, 1878. Vol. 3, p. 682.

³³ *i. e.*, abandoned.

³⁴ See also *Faustus of Byzantium*, iv, Chapter 4, and *Moses of Khorene*, iii, 20.

Blaise de Vigenere in the notes to his *Images et Tableaux de platte peinture de Philostrate Lemnien* remarks that when in Rome in 1566 he was invited to a dinner by Cardinal Vitelli, where the table was served "by at least thirty-four dwarfs, almost all hideous and badly formed."

With the opening of the Middle Ages the chief occupation of the crippled came to be that of court fool or jester. These personages almost universally found a place in the retinues of princes, and often in the households of noblemen.³⁹

These court fools can be divided under two classifications. In the first would come those creatures who by reason of deformity in body or mind were calculated to excite laughter and ridicule. In the second would be placed those chosen for a certain superficial quickness of wit and power of repartee. It is the first class with which we are especially concerned in our study of the attitude of the community toward the crippled and deformed; and they were to be found, unfortunately, in large numbers. The attire⁴⁰ of these jesters was distinctive, though varying slightly during different periods.

To judge from the prints and illuminations which are the sources of our knowledge on this matter, it seems to have changed considerably from time to time. The head was shaved, the coat was motley, and the breeches tight, with generally one leg different in color from the other. The head was covered with a garment resembling a monk's cowl, which fell over the breast and shoulders, and often bore asses' ears, and was crested with a cockscomb, while bells hung from various parts of the attire. The fool's bauble was a short staff bearing a ridiculous head, to which sometimes was attached an inflated bladder, by means of which sham castigations were affected.

The impressing of cripples into service as court fools continued and the institution was firmly entrenched for many years, despite many tendencies operating to improve the situation. Even a number of decrees passed by the Reichstag during the sixteenth century failed to obviate the practice. Not until the time of the Enlightenment was the final stage reached and the custom abolished.

Even after this time the court fool was still in vogue at the Russian court, Peter the Great having so many jesters of this type that it was necessary to divide them into classes.

When the Spaniards under Fernando Cortez accomplished the conquest of Mexico, court fools and deformed human creatures of all kinds were found at the Court of Montezuma.

It will be observed that the most significant fact developed by the history of the court fool is that during the period covered the victims of human deformity were regarded with ridicule and contempt. In the existence of such an attitude on the part of the general public, a sympathetic or merciful consideration can hardly be conceived.

During the latter part of the Middle Ages cripples came to be regarded superstitiously, this attitude being responsible

for a miserable existence for those deviating in any way from the normal.⁴¹

Ignorant people and scholars alike were influenced by such prejudice, and it is easily seen how cripples and deformed people were regarded as devilish monsters. Several circumstances gave rise to the general superstition. One of the most instrumental was the frequent confession on the rack by unmarried pregnant women that they had been seduced by the devil. This led indirectly to the belief that humpbacked and deformed children might have been of diabolical paternity.

Others regarded the deformed as victims of the wrath of God, and put them to death. King Francis I had burned to death at Avignon a woman who had given birth to a malformed child. Often, on the birth of a cripple or of a child with superfluous members, the attack of a hostile army was feared. There is a similar legend of Babylonian origin.

Martin Luther shared the belief, current at his time, in the theory of changelings. At the birth of an undesirable child it was believed that some diabolical mother had stolen away the right child and substituted her own offspring instead. Thus the child was known as a changeling. Cripples, rachitics and cretins were regarded as changelings. The idea was that if such children were maltreated sufficiently their mothers would come again to get them and leave the rightful children in their stead. It is easy to conceive the attitude which such a concept would engender. Luther⁴² also regarded malformed children as mere masses of flesh and considered that killing them was a work well pleasing to God.

Another phase of superstition affected the cripple—the belief that offspring could be harmed by "somebody" or "casting the evil eye" upon the pregnant mother. Parents were inclined to bring the deformity of their child into causal relation to a terrifying pre-natal experience on the part of the mother. In 1673 it is related that a citizen's wife was so frightened at the sight of a one-eyed, lame beggar that when she soon after bore a son, the infant lacked a hand and had a crooked leg. Many other similar instances can be found in literature.

One cripple, Thomas Schweieker (died 1602) of Schwäbisch-Hall, came to be highly regarded⁴³ on account of his learning and culture.

The first glimmer of hope for the welfare of the cripple began to appear in the eighteenth century, though the progress in this direction was very slow. The first measures did not in a strict sense mark the beginnings of care for cripples, but they operated to the ultimate advantages of those who, by

⁴¹ T. D. Herholdt, *Betrachtungen über den medizinischen Aberglauben und über Missgeburten im Allgemeinen. Appendix to Beschreibung sechs menschlicher Missgeburten*, Copenhagen, 1830, pp. 83-162.

⁴² Martin Luther. *Table-Talk*. (*Table-talk of the devil and his work—Changelings from the devil—History of a changeling at Dessau—Another history of a changeling.*) Theo. Kirchoff. *Grundriss einer Geschichte der deutschen Irrenpflege*, Berlin, 1890, p. 65-76.

⁴³ Martin Ulbrich. *Th. Schweieker*, Eisleben, 1909.

³⁹ K. F. Flögel, *Geschichte der Hofnarren*, Leipzig, 1789. Nick, *Die Hof- und Volksnarren*. Stuttgart, 1861, 2 vols. Ebeling, *Die Kahlenberger, Geschichte der Hofnarren*, Berlin, 1890.

⁴⁰ Walter Hepworth, *Encyclopædia Britannica*, Eleventh Edition, Cambridge, England, 1910, Vol. 10, pp. 614-615.

reason of their infirmity were cast upon the pity of their fellow-men. The actuating motive of provision in many cases, however, was utilitarian in character. One object was that all cripples might be confined so that they should not annoy the community by their deformed appearance.

Some of the many monasteries which had not been utilized since the time of the Reformation were thrown open and converted into orphan asylums, mad-houses, or penitentiaries. In the establishment of the various institutions the cripple was frequently considered.

Those handicapped by deformity were best provided for at a hospital for wretched and pauper invalids established at Pforzheim⁴⁴ in 1722 by Count Luitgard of Baden. This was later transformed by Count Charles Frederic of Baden into an orphan asylum, but made especial provision for young and old cripples. Kirmsse⁴⁵ quotes parts of the official ordinance on this matter as follows:

Cripples, by Margrave Charles Frederic of Baden. The princely ordinance of May 11, 1758, says on this:

"Since we now assume the place of a father to those who are orphaned in our territory or who are otherwise afflicted with grave misfortune, we cannot but desire special experience of our most gracious care to those who, in addition to such afflictions, are at the same time stripped of temporal wealth, and who are, therefore, stricken with double affliction."

"And the third class is composed of those who have such physical defects that they are an especial abomination and disgust to other men whenever they come into their sight. There are utterly misformed cripples and more of the sort."

IV. WORK.

"As many of these inmates as can be employed in any work shall be obliged to perform it, yet with reference to distinction of age, sex, and their physical infirmities. Here it is necessary to see in the first place—unless their deformities are slight—that there shall be sought out for them such tasks as may be performed in their rooms.

X. PUNISHMENT.

"Since the other inmates consist of crippled persons, no punishment but a few stripes will be allowed, although they may be chastened either with withdrawal of food or of drink or of both, but in every case after careful consideration of their circumstances."

DUTY OF PHYSICIAN.

"In the same (orphan asylum) are found the most utterly wretched of the entire country, including those sick persons who, in consequence of the cross of God laid upon them, are indeed a horror to other men, but all the more a true object of their pity. And, although, according to the measure of our human understanding they are counted among the incurable, nevertheless God has created many means to make their cross endurable. In their case, therefore, the physician must employ all his best science."

Of those capable of instruction it is noted merely that they should be sent to the school of the orphan asylum "when they

could stand it." The cripple department was abolished in 1808, probably because the room was needed for the insane.⁴⁶

Such provision for cripples, however, gave them asylum only and did nothing in a constructive way to better their condition, but the rise of the science of orthopedics was responsible for the ensuing improvement. It is true that one of the earliest Hippocratic treatises was orthopedic in character, but the attention which had been given to human deformity by the medical profession had, up to the time of which we are speaking, been inconsequential. One of the first to give extensive consideration to such work was Andry of Paris, who published⁴⁷ a two-volume work on orthopedics, illustrated. He encountered much skepticism. For example, Siebold, in his *Chirurgisches Taschenbuch*⁴⁸ claimed that the care of club-feet was impossible.

Another advance was made in 1780 when J. A. Venel, who was versed in both mechanics and medicine,⁴⁹ founded an institution for the deformed, at Orbe, Switzerland. Several other surgeons also did valuable work. The most complete books on the subject were by Jörg.⁵⁰

The theories of the various orthopedists were best put into practice in an institution and a large number of these were founded in the first decades of the nineteenth century; as, for example, those located at Paris, London, Leipzig, Lübeck, Berlin, and Vienna. One at Würzburg, established by Dr. Heine, gained especial fame, being the first of its kind in Germany.

The first institution for the deformed in Prussia was established at Berlin in 1823 by Dr. J. G. Blömer. This was designed for pay patients from among the upper classes, but indigent crippled children were also admitted. Between the years 1823 and 1827 he treated no less than 1179 cases of deformity, of which he claimed to cure 651. In a passage quoted by Kirmsse⁵¹ he thus describes the purpose and management of his institution:

An institution such as to be described has long been needed in our monarchy; all the more so because the forms of disability and sickness in question yield but indifferently to treatment outside of such a sanitarium. The difficulties in private practice are extensive and the curative methods can seldom be applied to as full an extent as is often necessary. Here belongs, among other things, the proper combination and joint application of medical and mechanical treatment, together with the requisite arrangement of suitable occupations for the sick, and the obviation of all factors tending to induce or further increase the physical deformities in question. Upon the persistent and accurate coördination of these conditions the possibility of a cure depends;

⁴⁶ Kelp. Irrenstatistik im Herzogtum Altenburg, *Allgemeine Zeitschrift für Psychiatrie*, 1847, iv, 587 ff.

⁴⁷ Berlin, 1744.

⁴⁸ Nuremberg, 1792.

⁴⁹ *Description de plusieurs nouveaux moyens mécaniques propres à prévenir, borner, et même corriger dans certains cas, les courbes latérales et la torsion de l'épine du dos.* Orbe, 1788.

⁵⁰ Ch. G. Jörg. *Ueber die Verkrümmungen des menschlichen Körpers*, Leipzig. *Die Kunst die Verkrümmungen der Kinder zu verhüten und die entstanden sicher und leicht zu heben.* Leipzig, 1816.

⁵¹ *Zeitschrift für Krüppelfürsorge*, iv, 13 ff.

⁴⁴ *Zeitschrift für Krüppelfürsorge*, Hamburg and Leipzig, 1911, iv, 10 ff.

⁴⁵ *Zeitschrift für Krüppelfürsorge*, Hamburg and Leipzig, 1911, iv, 10 ff.

that the elements are usually disparate is responsible for failure in many cases.

Since a large number of the sick who visit the institution are still young, special attention must be devoted to their education. That the invalids may not be impeded in their intellectual development by residence—which is often of long duration—at the institution, my endeavors were naturally directed toward providing for them training adapted to their ages and individual capacities—especially in view of the fact that the intellect is usually very acute and active in sufferers of this type. For still another reason I have been led to devote special attention to the subject of education. In ordinary life a certain obstinacy of character is usually attributed to those who suffer from bodily deformity—unfortunately not always without cause. A very natural cause is the mockery to which these unfortunates are often exposed by their frivolous playmates. They are shunned because their infirmity does not permit them to engage in many games of childhood and youth; they are restricted to their own company, and, imprisoned in their isolation, become not infrequently malicious. These faults, however, can be more easily removed during youth by continuous moral and intellectual training in an institution; more especially since the similarity of infirmity makes for much in common and demands mutual coöperation. The training is entrusted to a special teacher, who watches in a parental spirit over their morals and instructs them in varied school subjects. Naturally it must be my chief care that such an important position as that of teacher should always be filled by persons of intelligence and integrity.

Not desire of gain; but only the warmest interest in the matter itself, and a deep-seated longing to advance so far as possible the common weal, could lead me to establish an institution for the deformed in which even those of the most slender means can find the fountain of their healing and so look forward to as happy a future as possible.

The number of those seeking assistance, however, soon demanded a large institution. This at the same time placed me in a position further to extend my observations. Nevertheless, there were many difficulties to be contended with in connection with such an institution; the exactions demanded of the man who becomes its head are so considerable that long preliminary work and the greatest exertions were required before the institution could enter upon full activity. Considering the end in view, the earthly reward to be hoped for is extremely scanty in return for the manifold and ceaseless efforts expended; the sweetest recompense here is the consciousness of having laid a small gift on the altar of humanity, and of having opened to the poor no less than to the rich the fountain from which they may hope to draw, without expensive outlay, the healing of their infirmities.

Blömer had a workroom for making apparatus, bandages and artificial limbs. It is not known how long his institution lasted.

A similar institute was founded in Stockholm, Sweden, in 1827 by Dr. Aekermann.⁵² There was much difficulty encountered in overcoming public suspicion and distrust. Dr. Günther maintained an institution in Hamburg⁵³ during the years 1832-1837. While visiting Hamburg, Dr. Zine of Vienna became acquainted with this establishment and upon his return to Vienna founded a similar one,⁵⁴ May 1, 1838. This latter much resembled the institute of Blömer at Berlin.

In the meantime, however, there had been founded in Munich in 1832 the first comprehensive institution for the care and education of cripples. The Königliche Bayerische Zentralanstalt für Erziehung und Bildung krüppelhäfter Kinder was brought into being by an eminent philanthropist, Johan Nepomuk, and the principles then exemplified have, in general, been followed by most of the modern institutions which have since been established. A description of subsequent work, however, is outside the scope of the present article. In Denmark,⁵⁵ England,⁵⁶ Italy,⁵⁷ as well as in Germany⁵⁸ and the United States,⁵⁹ extensive systems of care have been built up, and in almost every civilized country of the world there is made some provision for the welfare of the cripple.

The community has now realized to a very considerable extent its responsibility toward the cripple and the early vicissitudes to which the deformed were subjected are indeed a matter of history.

⁵² C. J. Eckström. *Ars-Berättelse om Svenska Lakäre-Sällskapets Arbeten*, Stockholm, 1829.

⁵³ H. Gleiss. *Lebenserinnerungen von Elise Averdieck*, Hamburg, 1908, pp. 48-50.

⁵⁴ Erster Bericht, 1853; Jahresbericht . . . für 1853, Vienna, 1854; *Correspondenz-Blatt der deutschen Gesellschaft für Psychiatrie*, 1854, p. 16; *Die angeborenen Verrenkungen*, Vienna, 1845.

⁵⁵ Douglas C. McMurtrie. The Copenhagen Institution for Cripples, *Boston Medical and Surgical Journal*, Boston, 1911, clxv, 794-798.

⁵⁶ Douglas C. McMurtrie. Crippled Children in the English Public Schools, *New York Medical Journal*, New York, 1913, xevii, 188-199.

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⁵⁸ Konrad Biesalski, *Umfang und Art des jugendlichen Krüppeltums in Deutschland*. Hamburg and Leipzig, 1910. Also the files of the *Zeitschrift für Krüppelfürsorge*.

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FIRST ANNOUNCEMENT IN REGARD TO THE PROJECTED CELEBRATION OF THE 25TH ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL.

BALTIMORE, October 18, 1913.

Dear Doctor:

At an informal gathering of former officers and members of the medical staff of the Johns Hopkins Hospital upon October 10, 1913, it was unanimously agreed that the 25th anniversary of the opening of the hospital should be commemorated by appropriate exercises of a special character at the hospital during the first week of October, 1914. It was further decided that the trustees of the Johns Hopkins Hospital and the Johns Hopkins University, officers and members of the hospital staff and all teachers and former students of the medical department of the university should be cordially invited to participate in a general reunion at that date.

The commemoration exercises are planned to extend over a period of three or four days at a time when it may be expected that the lectures on the Herter Foundation will be delivered. Dr. William Osler has promised to be present. In addition, there will be commemorative addresses and a scientific programme with clinics, demonstrations and hospital rounds conducted by present and former members of the staff. It is anticipated that the James Buchanan Brady Urological Institute can be opened with appropriate ceremonies at the same time. A memorial tablet to the late Dr. John Hewetson, which is nearly completed, will be placed on the walls of the general dining-room. It has also been suggested that a similar tablet in memory of all deceased members of the house staff be prepared and placed in the hospital. There will be dinners, class reunions and receptions during the week.

All details of the celebration have not been fully arranged, but the work of preparation will be placed in the hands of competent committees. The co-operation and presence of former members of the hospital or medical school staff and of former students or graduates of the medical school is cordially invited. Circulars

presenting full details of the events of this commemoration week will be sent from time to time. This communication is designed to give each person who is interested a timely notice of our plans.

WILLIAM H. WELCH,

WILLIAM OSLER,

WILLIAM S. HALSTEAD,

HENRY M. HURD,

HOWARD A. KELLY,

Committee of Announcement.

The Committee will be pleased to receive an acknowledgment of this circular together with suggestions as to the proper and fitting celebration of this anniversary from all persons who receive it.

Letters may be addressed to Dr. Henry M. Hurd, 1063 Calvert Building, Baltimore, Maryland, or to Dr. Rupert Norton, Secretary of the Committee, The Johns Hopkins Hospital, Baltimore, Maryland.

NOTES ON NEW BOOKS.

Eye-Strain in Everyday Practice. By SYDNEY STEPHENSON, M. B., etc. (New York: Paul B. Hoeber, 1913.)

This is an interesting series of papers, republished from various English medical journals, showing the apparent effect of eye-strain in producing various reflex neuroses. Although too much stress has been laid possibly on the effect of eye-strain in causing a great variety of neurasthenic, hysterical and other functional (?) symptoms, yet there is no doubt that eye-strain is a causative factor at times in illness of various sorts and degrees of severity, and this little book is of value to the general practitioner by drawing his attention to the necessity of examining the eyes when he meets obscure nervous symptoms which do not give way to ordinary treatment.

Practical Bacteriology, Blood Work, and Animal Parasitology. By E. R. STITT, M. D., etc. Third Edition, Revised and Enlarged. Illustrated. \$1.50. (Philadelphia: P. Blakiston's Son & Co., 1913.)

By using different sizes of type the author has been able to add considerable new material without materially enlarging the size of this pocket manual, which has distinct merits, but should be used only in conjunction with larger works on the same subjects. For its size it is the best book of its kind and a good one, for it is written by a thoroughly well-informed and well-trained physician. For students its danger or defect lies in its compactness. There is so much that is not yet definitely settled in these branches of medicine, that Stitt's clever presentation of his subjects may, perhaps, give beginners false ideas as to the difficulties inherent in the study of bacteriology, etc.; none the less it is a book we are glad to note has met with a deserved popularity.

Syphilis and the Nervous System. By DR. MAX NONNE. Authorized Translation from the Second Revised and Enlarged German Edition by CHARLES R. BALL, M. D. Illustrated. \$4. (Philadelphia and London: J. B. Lippincott Company, 1913.)

It is often the case that not the best or most serviceable books are translated from one language into another, and it is fortunate for Americans, therefore, that Nonne's work has been capably translated by Dr. Ball. It is a book which students and practitioners will find very helpful. Its chapters on tabes and dementia paralytica—these two common diseases—cover the ground thoroughly, and will make the path of the student easier in his study of the differential diagnosis between these and other diseases with oftentimes similar symptoms. Other chapters are as good as these two, to which we call attention merely as the conditions discussed are the more common and prevalent syphilitic affections.

The author's experience has been very large, and the cases he reports are of unusual interest. The general practitioner will do well to buy and study this book—he cannot know too much about syphilis, most know far too little—and he will find the perusal of Nonne most profitable.

Tuberculin Treatment. By CLIVE RIVIERE, M. D., etc., and EGBERT MORLAND, M. B., etc. Second Edition. \$2. (London: Henry Frowde and Hodder & Stoughton, 1913.)

This is a second edition, indicating a well-deserved popularity of the work. Corrections and additions have been made through-

out, the chief alterations being under the headings, "The Tuberculin and their Preparation," "Tuberculin in Mixed Infection," and "Ambulant Treatment of Phthisis." These three headings are a decided improvement on the first edition—all three being clear, concise and to the point.

The book should be of interest and assistance not only to physicians who are making a specialty of tuberculosis but also to those in general practice to whom many tubercular patients are referred on leaving a sanatorium or dispensary supervision.

The authors are to be complimented on their work which ought to meet with popular approval.

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Physician

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BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

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REMARKS ON CASES RECEIVED IN THE HENRY PHIPPS PSYCHIATRIC CLINIC.*

By DAVID K. HENDERSON, M. D.,
Resident Psychiatrist, The Johns Hopkins Hospital.

During the eight months from May 1 to December 31, 1913, in which The Henry Phipps Psychiatric Clinic has been in operation, 238 patients have been admitted. Ninety-six or 40 per cent of these have been from states outside of Maryland, fifteen or six per cent from Maryland, outside of Baltimore, and the remaining 54 per cent from Baltimore City.

The Psychiatric Clinic is intended to serve as a place for the study and diagnosis of *all* forms of mental disorder, and for the treatment of those who may be expected to benefit from the forms of treatment practicable in such a type of hospital. The range of cases includes the functional and the organic, the acute and the chronic, the pay patient and the free patient.

The number of patients admitted up to the present has been the limit of what we were able competently to handle, considering the care and caution needed in the selection of the nursing force. Many applications have had to be refused, but

* Paper read at a meeting of the Baltimore City Medical Society, February 6, 1913.

it is a matter of great satisfaction that we are enabled to say that no patient from Baltimore has as yet been refused admission because he could not afford to pay anything.

It has seemed very desirable to us to give the physicians of Baltimore a somewhat clearer idea of the principles we follow in admission of our cases, and it is therefore a pleasure to use this opportunity to make an appeal to you for cooperation in an important matter, namely, that of helping public opinion to align itself more and more in keeping with the changing conceptions of modern psychiatry.

The standard used by us is that of considering as suitable for admission any patient in whom a mental break-down is induced by either mental or organic factors, from so-called nervousness and instability to the most pronounced cases of mental disorder. One point we do stand out for, and that is the demand for a reasonable amount of cooperation both on the part of patient and family.

It is our wish as far as possible to eliminate the mere question as to whether the patient is insane or not; the

important point of distinction is: Does the patient or at least the family show a reasonable spirit of cooperation?

To give you a very summary idea of the type of cases it will suffice to say that among the 238 cases received,

14	women	and	40	men	had	organic	disorders.
22	"	"	17	"	were	cases	of various psychoneuroses.
23	"	"	18	"	were	cases	of depression.
6	"	"	21	"	were	cases	of excitement.
35	"	"	21	"	were	cases	of dementia præcox and allied states.
6	"	"	11	"	were	cases	of toxic psychoses.
4	"	"	9	"	were	cases	of constitutional psychopathic disorders.

In only 8 of these cases was commitment resorted to.

Public opinion still makes a very exaggerated contrast between simple mental difficulty and insanity, and unfortunately many physicians tend to bewilder the public still further by using that very misleading term "borderland case." It seems to be a wide-spread misconception that only so-called "borderland cases" are admitted to the Psychiatric Clinic; another misconception is that only acute cases are received, and a third and rather negligible one is that the Clinic is chiefly a place for the training of defective children.

The name "borderland" seems to me to be a very dangerous one, and one very fruitful of error. I suppose that it is its ambiguity that is so appealing—as the term eczema is in skin diseases—and on that account it is used to denote cases in which the diagnosis is more or less doubtful. One's experience either with the psychoneuroses or with the psychoses proper need not be extensive before one begins to appreciate that there is no definite dividing line between these conditions, and that too frequently the patient tends to get quite an erroneous view of his condition which is hard to eradicate. The line of division lies chiefly between cooperative and non-cooperative states, and not between any supposed standard of sanity or insanity.

Our main opportunity for progress in combating mental disorders is to facilitate as much as possible the admission of voluntary patients during the stage of capacity to cooperate—a tendency which is well exemplified by the numerous voluntary admissions to all the progressive institutions around us. The family physician more than any one else is the best person to point out to the families and patients how success or failure in the treatment of a case depends to a tremendous extent upon the degree of cooperation.

It will not be necessary to discuss the general methods of work with our patients, the special treatment of the specific cases, the treatment for drug and toxic cases, the hydrotherapy, gymnasium, and occupation treatment, and the efforts to help the patients to attain to a mental readjustment. But it may be of some use to depict briefly a few cases in which the cooperation of the family physician would be of the utmost importance, and a few others illustrating the range and aims in the treatment of cases calling for a mental

readaptation. Some of these cases may also suggest how important it is to make a very close and diagnostic study of the symptoms so that grievous mistakes may be avoided.

A young married woman, 30 years old, was admitted to the Clinic on May 19, 1913, with a history of having lost weight (50 lbs.), of persistent vomiting, air hunger, and occasional catheterization. She was admitted to a quiet ward, but owing to her strenuous objections had shortly to be moved to a private room. She lay quietly in bed with a smiling expression, and talked freely about her complaints. She frequently would take deep inspirations, followed by a long sighing expiration and said: "When I breathe naturally it does not satisfy me, I must take deep breaths—it seems as if the breath just goes to here" (pointing to the middle of the sternum). As soon as one could get her interested in a conversation, however, her respiratory difficulties considerably abated. In addition to her respiratory difficulties she refused to take anything to eat except a little cracked ice and milk from a medicine dropper. A careful examination of her physical condition failed to elicit any basis for her complaints. The history of the case in brief showed that she had been a healthy child, who apparently had developed normally, and married at the age of 19 years in 1902. In June, 1905, 3 years after marriage she was admitted to the Maternity Ward of the Johns Hopkins Hospital, and was at that time 5 months pregnant; but, what is of more immediate interest to us, it is also noted in the history that she showed considerable respiratory difficulty, especially in the presence of a doctor or nurse. These symptoms, even at that time, were diagnosed as being neurotic in origin.

Following the birth of her child on November 15, 1905, she remained well for a very short time, but then commenced to complain of vague pains, on account of which she underwent three operations—in 1908, 1909, and January, 1913, for adhesions. In September, 1912, however, vomiting, which soon became persistent in character, developed. This vomiting was at first thought to be due to another pregnancy: but, after that diagnosis had been ruled out, pelvic adhesions were blamed for the vomiting, which was considered to be of reflex origin, and so finally in January, 1913, the last operation was performed. Following this operation she did not vomit for 15 days; she returned home, but 3 days later vomiting again started so that until the time of her admission to the Clinic she had been existing on a small quantity of "lozak" or a little ice-cream.

During all these months at home she had been confined to bed, and made life unbearable for everyone in the house; her husband's capacity as a workman was seriously interfered with, and her family physician would be summoned both night and day to console her and to administer morphia so that she might get a little sleep.

No time was given us to make an analysis of this case, but from the history which has been given, many psychogenic features are evident. During the two and a half days she was in the Clinic she was exceedingly discontented, asked to be taken home all the time, and owing to the fact that those who were closely associated with her would not take a definite stand, the patient had to be discharged. The case clearly shows how important an early diagnosis of psychogenic factors would have been, and how necessary the firm advice of the family physician.

A second case was that of a young married woman, 23 years old, who on admission had a twitching movement of the left side of her face, frequently protruded and withdrew her tongue, and lay in a somewhat trance-like state, usually with her eyes half closed. She looked pale and anguished, and frequently put her hand over the region of her heart. She answered questions in a sing-song, irrelevant way, and repeated the same thing over and over again. At times she tended to assume an opisthotonos position, and frequently tried to vomit. She did not react to pin pricks anywhere

over the body or face, willingly put out her tongue to be pricked, but her corneal reflexes were present on both sides.

The history of the case showed that three months previous to her admission to the Clinic the patient's sister had died in a hospital from nephritis. The patient had been greatly attached to this sister, frequently talked about her, and following her death visited her grave every day, rain or shine. About one month after her sister's death she consulted the family physician for nausea, complained of all the symptoms from which her sister had suffered, and thought too that she had nephritis. Two months later and two days previous to her entrance to the Clinic she complained of pain in the left side of her abdomen, refused to talk, would hold her breath at times, and twitching started in the left side of her face and in both arms. Two days following admission the patient was much better but refused to cooperate in a thorough analysis of her case, said that she did not want to stay in a hospital as her sister had died in one, and consequently five days after admission the patient was taken home by her relatives much improved, but far from having learned to understand and protect herself for the future.

A third case which emphasizes the same points as the previous two was that of a young married woman of 30 years of age, who was admitted to the Clinic in an excited, hallucinatory state in which she saw God and felt compelled to do everything that he told her to do. She seemed fearful, blamed herself for having sinned, told about a clandestine love affair with a physician and begged God not to send her to hell.

The history showed that she had been a healthy girl who had developed normally. In 1910 she married, but owing to a vaginismus had never been able to have sexual relations with her husband, which was a source of considerable dissatisfaction to her.

For about 10 days before admission she had a fever with a temperature elevation varying from 103° to 104° F., for which no adequate cause could be determined. No mental symptoms showed themselves until 2 days previous to admission when immediately after receiving communion she began to talk about her sins having been forgiven, told how the family physician had shown affection for her, and of how she had had two children fifteen minutes apart without any pain. Later because God told her to do certain things she became very violent and abusive.

During her six days residence in the hospital the patient improved considerably, but then the husband despite every argument insisted upon taking her home, even though the patient still believed that she had actually seen and talked to God, and while she still maintained that she heard voices telling her certain things.

Such cases I suppose would be called by many "borderland" cases, but the striking feature about them all has been their total lack of appreciation of the entire situation, and that in itself should be sufficient to make one take an ominous view of such cases. It seems to me that the only way, at least the only satisfactory way, in which these cases can be treated is to have the thorough cooperation of the family and of the family physician, so that legal commitment by two physicians might be urged in the case of absolute necessity. Such patients are essentially mental cases, and that being so it is entirely wrong to allow the patient to dominate the situation and at the same time play the part of both physician and patient. It is usually such cases as the above who most unfortunately have been assured before their entrance to the Clinic that they will not be associated with "real mental patients," but with other "borderlands" like themselves, and when their suspicious minds discover evidence

of supposed insanity in others, then they feel deceived, and the trials of management come to the front.

In all three cases the psychogenic material is self-evident, and it is just such cases that can be exceedingly benefited by means of a thorough analysis, provided that physician and family help the patients to see themselves and the Clinic in the right light.

In addition to the cases already reported, may I be allowed to mention two other cases that illustrate even more conclusively the great necessity for thorough cooperation?

Both of these were cases which had been allowed to drift along for several years, were eventually brought to the Clinic, but after an exceedingly short stay were removed owing to the fact that the relatives thought that the patients' feelings deserved more consideration than the patients' welfare. One of these was a young man 22 years old, whose mother went so far as to enter him under a fictitious name and at first refused to give his address because she did not want anyone to know where he was. The patient had never been able to do any steady work, was evasive and suspicious in his general attitude, which condition had persisted unchanged for three years. His mother removed him on the day after admission because she could not bear having him in a ward with other patients.

The other case was that of a single woman 50 years old who was admitted in an utter state of dejection and helplessness with a history of a self-accusatory trend for having committed unpardonable sins, and thought of suicide. She came from a poor stock, had been interested particularly in the spiritual side of life, and, as is not unusual in such cases, had indulged freely in auto-eroticism from the age of five years. She was a patient for whom a good deal might have been done, but as soon as her relatives heard that she was in a hospital for treatment of nervous and mental disorders, they heartily approved of the patient's desire and determination to return home. These are mishaps which we can only hope to correct if we physicians can give a less confusing view of the purposes of the hospital and can disregard the old division of sanity and insanity.

To consider for the sake of contrast a more hopeful side of things, I want now to show how when one has good cooperation excellent results may be obtained, even in complex cases, by means of the proper study of the factors requiring readjustment. I shall again illustrate the point, which I wish to demonstrate, by reference to a case.

A young unmarried woman, 24 years old, on admission to the Clinic had a worried, disconsolate expression, and gave a history of having had fainting attacks at the age of 10, 13, and 21 years. For three months previous to admission she had been at home in a nervous condition, and during that time had frequent "fainting attacks." On coming to the Hospital the patient was first admitted to the general ward, but during her three weeks residence had two convulsive attacks, in which she screamed, assumed an opisthotonos position, did not wince when stuck with a pin, and called on some men whom she imagined were present to leave her. It was on account of these spells and on account of the fact that she had not reacted to general medical treatment that the patient was transferred to the Psychiatric Clinic.

The patient described herself as always having been of a secretive nature and an exceedingly conscientious student while preparing herself for work as a missionary. It seemed impossible to get at the basis of her trouble simply by straightforward talks, and therefore association tests and an analysis of her dreams were undertaken. By means of this it was soon revealed that her fainting attacks had occurred in relation to the intense conflict about her auto-erotic behavior which had troubled her since infancy. The attacks were usually precipitated by some external reference, *e. g.*, social problems, difficult work, or imminence of her secret knowledge being discovered. After the general biological aspects of the natural instinctive life had been explained to the patient, and a plan of readjustment had been outlined and partially carried out, the patient was tremendously relieved. She was discharged 14 days after admission with a new point of view and with a safe and sound understanding of how to handle herself.

Here then was a case which had not reacted to general medical measures, but in a short time an excellent result was obtained by means of procedures which demand the training and patience of the specialist.

Before concluding, I want to cite still one more case to show how it is not the acute cases only which react to treatment, but also how occasionally long standing cases when subjected to intensive treatment by a careful going over of the causal factors may show a remarkable improvement.

A young lady, 27 years old, was admitted to the Clinic on June 27, 1913, in a rather inaccessible and impulsive condition. She kept repeating the same thing over and over again, continually said that she must go home and whenever anyone entered or left the ward, made a bolt for the door. She smiled and giggled in a stereotyped way, showed a great deal of facial grimacing, and could not be got to cooperate in a satisfactory mental examination, usually replying to questions with such an answer as "I don't know—I must go." She could not give any definite account of how she had been during the last two years. She seemed puzzled by the whole situation, would not recognize physicians whom she had known formerly, and apparently seemed the victim of inaccessible imaginative ruminations and blind impulses, with the characteristic features of dementia præcox.

The history of this case showed that this patient had always been a conscientious, quiet girl, who in some ways might have been characterized as precocious. She was brought up in absolute ignorance of sexual matters, and at school was told of a number of things which she felt that she ought to have known, and in consequence of which she accused her mother of having exposed her to ridicule. Previous to this, in 1904, she is described as having two tantrums of laughing and crying of short duration. In 1905 she went to school in Europe, but then became discontented, was very nervous, and while on board the ship returning home claimed that she was pregnant, and that the ship surgeon had taken advantage of her. Immediately after landing she was put in a private institution, where she is described as having been suicidal and impulsive, and having had a number of delusions. In 1907 some improvement occurred in her condition which lasted until 1911, when she again passed into a state of fancies, refused nourishment and kept repeating the same thing over and over again.

Here was a patient whom everyone would be inclined to designate as an absolutely hopeless case, but in whom a remarkable improvement has taken place during her residence in the Clinic. She is now able to employ herself in many useful ways, goes shopping, and behaves in general like a normal person. The full knowledge of the factors in the patient's life and of her reactions seemed to justify the patient's receiving hospital treatment, which was made possible because the parents were willing to cooperate in every way. It goes without saying that especially the period of improvement and convalescence is of the greatest importance for intensive treatment and for the laying of a safer foundation for the patient.

Enough has now been said to show how important it is to get away from using terms such as "borderland," "acute," "chronic," "insane," and "not insane," and that the only satisfactory basis on which patients can be received is one of willingness to cooperate, if possible, on the part of the patient and above all things on the part of the family.

ESSENTIAL SIALORRHEA IN A DOG, CURED BY EXCISION OF THE PAROTID, SUBMAXILLARY AND A PORTION OF THE SUBLINGUAL GLANDS.

By JOHN W. CHURCHMAN, M. D.

(From the Laboratory of Surgery, Yale University.)

In an exhaustive study of sialorrhœa by André,¹ essential sialorrhœa is said to be very rare, "if indeed it exists." It is defined as a neurosis in which sialorrhœa is the only or predominating symptom and is said to follow traumatism or a slight infection, as in a case of Ball's, in which the condition developed after a cervical adenitis.

In the case here reported, sialorrhœa of the most extreme type developed without apparent cause; it was accompanied by advanced and progressive asthenia and cachexia; excision of the glands was followed by complete cure of the sialorrhœa and

restoration of the moribund animal to normal; and examination of the excised glands showed no changes save an increase in size. The somewhat vague term, essential sialorrhœa, seems therefore sufficiently justified as descriptive of the condition present.

The case was referred to me by a veterinarian, Dr. H. L. Tower, of New Haven. The animal was a Boston bullpup, a much-prized family pet. He had been healthy at birth, but shortly afterward began to drool saliva. At first this was the only symptom, but anorexia gradually supervened; and soon attacks of vomiting came on, the immense amounts of saliva swallowed causing constant gagging and frequent expulsion of

¹ André: De la sialorrhée. Paris Thesis, 1898.



FIG. 1.—Condition of dog before operation.

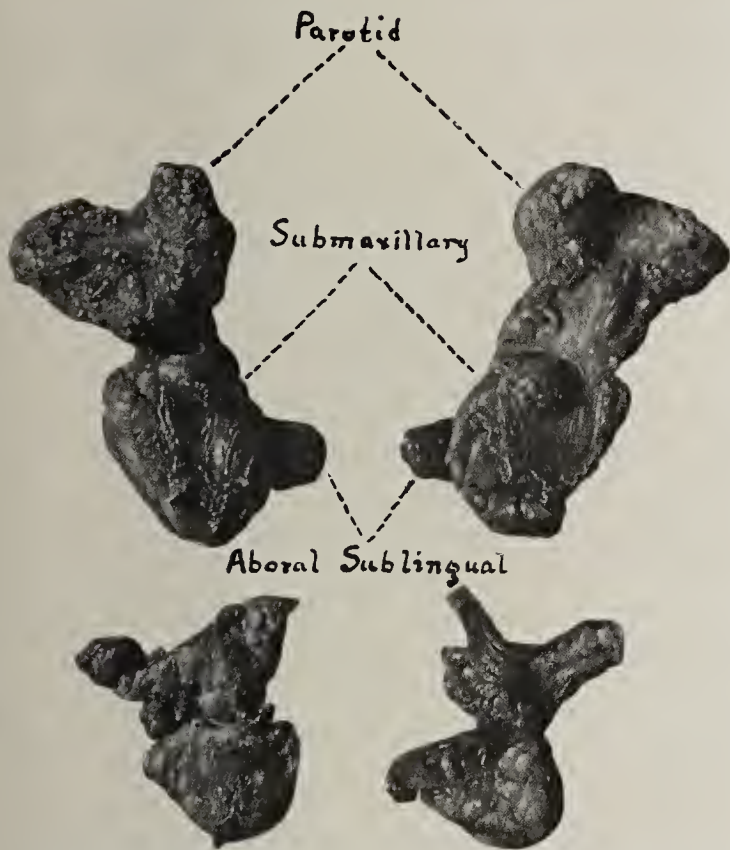
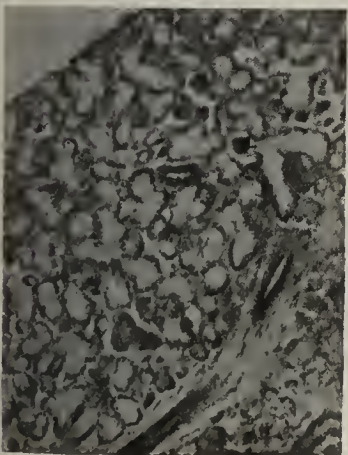
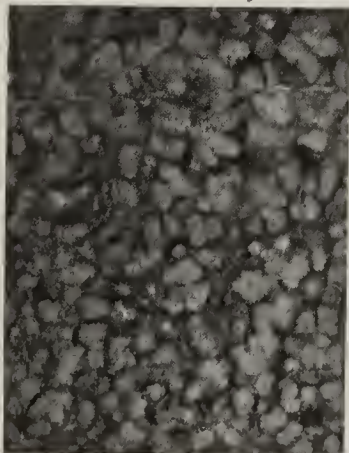


FIG. 3.—Removed glands (above), compared with glands from a normal pup (below).



a



b

FIG. 6.—Low power microscopic sections of the submaxillary gland: *a*, from the case of Sialorrhea, and *b*, from a normal pup.

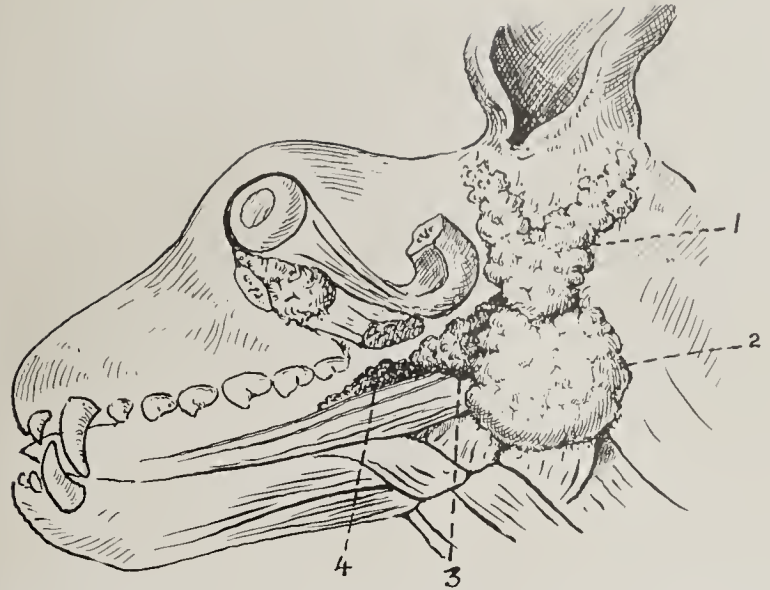


FIG. 2.—Sketch of the salivary glands of a dog; modified from Ellenberger and Baum, showing the glands removed, in the case reported.

1. Parotid gland.
 2. Submaxillary gland.
 3. Sublingual gland—aboral portion.
 4. Sublingual gland—oral portion.
- 1, 2 and 3 were excised; 4 was left.



FIG. 4.—Condition of dog 7 months after operation.



FIG. 5.—Condition of dog 7 months after operation.

the saliva from the stomach. The animal refused food, became spiritless and was dying of asthenia and starvation.

On admission the dog, an affectionate little animal, was little more than skin and bones. He weighed 3375 gms. (see Fig. 1, which really fails to do justice to the emaciation). He was quite weak, moving about languidly in search of a sunny spot to lie down in. The jaws were constantly dripping saliva and the bed made for him was kept soaked. Every little while large amounts of saliva were vomited. He could be made to take food only with difficulty, and was altogether a pitiable object to behold. Abdominal examination was negative and no signs of paralysis or other nervous lesions were discovered. Greatly enlarged salivary glands could be felt beneath the lower jaw, reaching in a crescent from the root of one ear to the root of the other. No chemical analysis of the saliva was made; nor was its ferment coefficient determined.

Under ether, excision of both parotids, both submaxillaries and both sublinguals, was done. The oral portion of the sublinguals was left (see Fig. 2). The glands were evidently enlarged (see Fig. 3), but were otherwise unchanged. The postoperative convalescence was without event. The wound healed nicely and there was almost no general reaction.

For a few days following operation a rather more than normal amount of saliva was secreted, but nothing that could be called sialorrhea was observed. The dog's bed remained dry, there was no gagging or vomiting; and on the tenth day the dog, though still weak, was able to be taken home. Here rapid recovery began and has since continued. Salivation has ceased entirely; the dog is in every respect normal. He runs and plays actively, eats well, and now weighs 6770 gms., nearly twice what he weighed on admission to the laboratory (see Figs. 4 and 5). He is still small in frame.

The literature of sialorrhea has been completely reviewed by André. On account of the not ready accessibility of his publication and the rarity and interest of the condition it may be useful to present a brief synopsis of André's findings.

If sialorrhea be classified according to etiology, the following types may be recognized:

1. Essential sialorrhea. By this term is understood a neurosis in which abundant secretion of saliva is the only or predominating symptom. It is rare, if it exists.
2. Nervous sialorrhea. Here are grouped the cases which depend on:
 - a. Epilepsy.
 - b. Hysteria. Many of the cases fall in this group. The excessive salivary flow may be determined by an emotion, a sharp odor, an acid taste, etc. It may last months and make the prognosis grave. Bloody salivation has been observed by Mathieu, the blood coming from the glands themselves.
 - c. Neurasthenia.
 - d. Exophthalmic goitre and myxœdema.
 - e. Rabies.

3. Sialorrhea due to an organic nervous lesion. It is seen in:
 - a. Paralysis agitans.
 - b. Diseases of the medulla:
 - i. Labio-glosso-pharyngeal paralysis.
 - ii. Progressive muscular atrophy, poliomyelitis and other diseases involving the labio-glosso-laryngeal centers.
 - c. Diseases of the cord with progressive involvement.
 - d. Diseases of the brain: hemiplegia, Jacksonian epilepsy, general paralysis.
 - e. Mental diseases: acute mania, idiocy, dementia, hypochondria.
 - f. Affections involving the cranial nerves, particularly the facial. Sialorrhea only occurs when the lesion is central, for division of the facial causes decrease in salivary secretion. The sialorrhea is due to the removal of cerebral inhibition on secretion. In tic douloureux the salivary crisis may accompany, follow or replace the painful crisis.

4. Sialorrhea with visceral disease.

- a. Digestive:
 - i. Diseases of the buccal cavity: stomatitis, parotitis, dentition in infants, etc.
 - ii. Stomach. Sialorrhea may accompany hyperchlorhydria. In some of the cases the saliva accumulates in the esophagus and is vomited, to be followed by vomiting of gastric contents (elective vomiting).
 - iii. Intestinal parasites.
 - iv. Diseases of the pancreas.
 - v. Diseases of the larynx: cancer, etc.
- b. Diseases of the genito-urinary system.

In women, sialorrhea may appear at various periods in the genital life: at the menopause, at the monthly periods and particularly during pregnancy ("This symptom in a young woman ought make us suspect pregnancy"—Tarnier). The sialorrhea in pregnancy has in some cases disappeared after a fictitious abortion.

5. With infections and intoxications.

Examples are the sialorrhea seen in mumps, smallpox, malaria, gout, etc., and the critical salivation of pneumonia. Of the substances elaborated in the body and excreted, some (like bile and sugar) are not found in the saliva, but uric acid is occasionally found there. Some substances eliminated in the saliva excite salivation only feebly or not at all (*e. g.*, potassium iodide); others, like mercury, are true sialogogues.

Histopathology.—Of the histopathology of sialorrhea little or nothing is known. The well-known changes described by physiologists and pathologists as the result of prolonged physiological stimulation have usually been assumed to be present

in the condition of secretory activity which expresses itself clinically in sialorrhea. So far as I am aware no resection of the glands has previously been done for this condition; and a description of the specimen removed in this case is therefore given.

There was obvious macroscopic enlargement of the salivary glands, which formed, as I have said, a crescent reaching from ear to ear. The comparison of the glands removed, with a similar specimen from a healthy pup of about the same size and age is shown in Fig. 3. The glands removed weighed 28.2 gms.; the normal glands 7.5 gms. When examined with the low power, the alveoli with their basement membrane are seen to be retracted from the interstitial tissue. This is not

due to atrophy of the alveoli, which are well developed, nor to atrophy of the individual cells, which seem to be as large as those of the normal gland. The interstitial tissue is actually diminished in amount and forms a much smaller proportion of the whole section than in the normal gland. The inter-alveolar spaces are, therefore, more evident and the glands less compact in structure than the normal glands. There is no definite change in the high power picture of the secreting cells, nor of the demilunes. The mucous cells are large, the lumen of the alveoli very small, the nuclei lie at the base of the cells, and the protoplasm fails to stain. The picture, strangely enough, is that of the loaded or charged state usually associated with freedom from secretory activity (see Fig. 6).

OBSERVATIONS FOLLOWING THE USE OF COLLARGOL IN PYELOGRAPHY.

By CECIL W. VEST, M. D.,

Late Resident Gynecologist, The Johns Hopkins Hospital.

Abdominal surgeons and urologists are often called upon to diagnose renal conditions and tumors or to exclude the upper urinary tract from the other organs considered. In this field, as in all other branches of medicine, anything which will aid in differential diagnosis is eagerly employed. Recently the plan of injecting the renal pelvis with collargol and then taking an X-Ray picture has been used in urinary clinics. From such a radiogram, the outline of the upper urinary tract can readily be made out, and this is of marked value in determining the size, shape and position of the renal pelvis and ureter.

For the past three years this method has been followed in the gynecological department of the Johns Hopkins Hospital, and our attention has been called forcibly to symptoms and conditions, which at times follow the use of collargol. In many of the public ward and dispensary cases so treated here, no symptoms whatever have been noted as a result, but a few patients have caused us some uneasiness by their reactions.

The technique used by the author has been practically uniform in all cases. After catheterizing the ureter desired and measuring the capacity of the renal pelvis, the patient is made ready for an X-Ray picture; then the renal pelvis is injected, the photographic exposure made and the collargol allowed to run out, so that it does not remain in the renal pelvis more than two or three minutes. The injections * are

made slowly and carefully with a piston syringe. When the patient first feels a fullness or tightness in the side, the injection is stopped. In order that as small an amount as possible of the collargol might remain in the pelvis, for the past six months we have irrigated it with sterile water. A 15 per cent solution of collargol is used ordinarily, but a 10 per cent solution has been tried in a few cases. No difference in the symptoms has been noted with the weaker solution, while a better shadow, especially in fat patients, is obtained with the stronger solution. Tennant † used a 25 per cent solution in a second injection.

The collargol is never sterilized and is always thoroughly shaken before the injection. In many cases the material was warmed before using. The solution is usually used within one or two days after preparation, but in some cases it had been kept for ten days or two weeks in a tightly stoppered bottle from which evaporation was prevented.

In the histories of the six cases that I report, the constitutional disturbances noted are all recorded. The chief complaint in the injection, whether with water or collargol, of the renal pelvis is pain, which occurs probably in one-fifth of the cases. The pain is persistent, often lasting from one to three days, while in one of my cases it was necessary for the patient to remain in bed ten days following the injection. Nausea and at times vomiting are associated with the renal pain. In three cases there has been a rapid rise of temperature following the

* To avoid possible injury to the kidney from an injection made under pressure, the plan of allowing the fluid to run into the renal pelvis by gravity has been tried. An instrument for this purpose is shown in Oehlecker's¹ article; it is quite simple, consisting of a glass measuring cylinder from the lower end of which a piece of rubber tubing about 4 ft. in length leads to the renal catheter. The cylinder can be placed at any desired height.

Thomas,² of the Mayo Clinic describes a similar instrument for the same purpose. A Y-shaped tube is attached to the lower end of a titrating buret. To one end of this tube is attached a piece of rubber tubing 4 ft. in length. A needle to be inserted in the renal

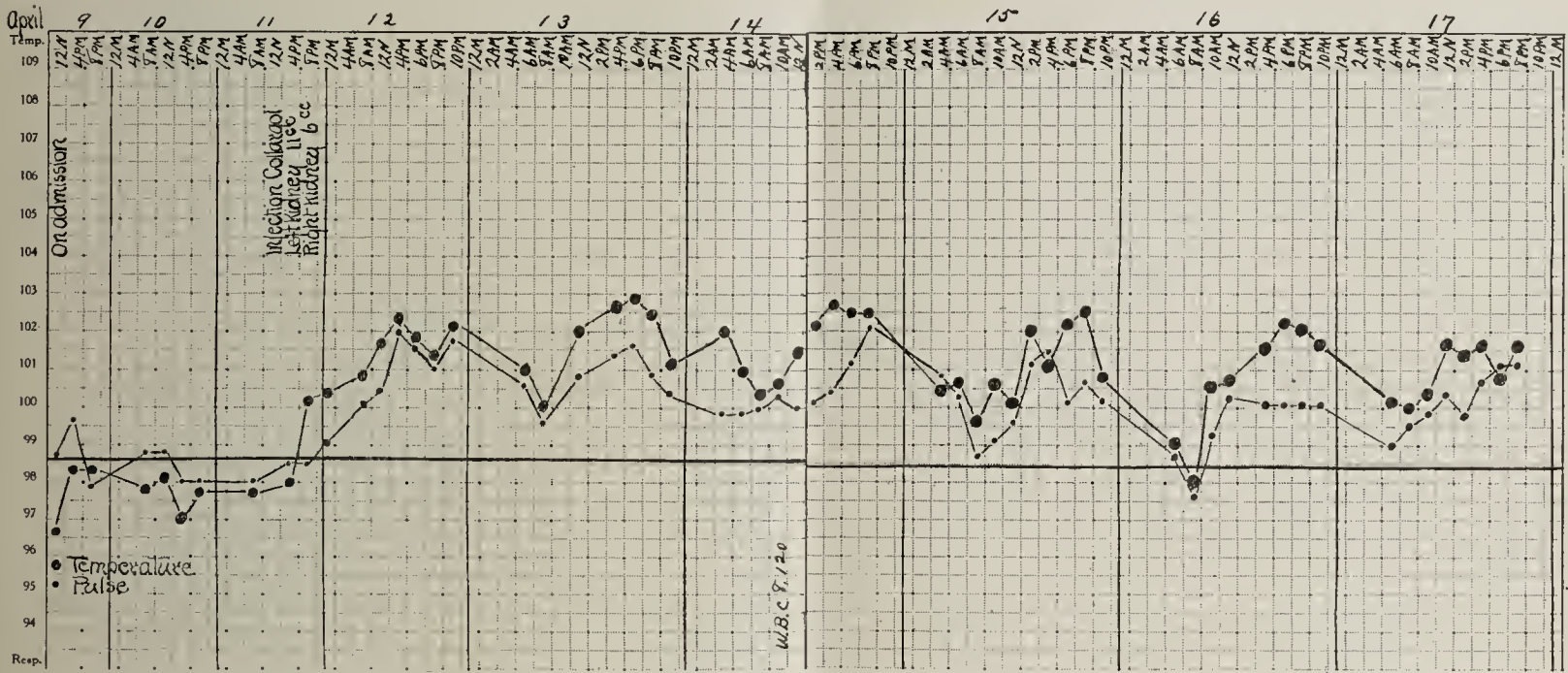
catheter is fastened to the other end of this tube. The other arm of the Y connection empties the buret which is supported by a telescoping stand.

† Here³ the author has graphically shown by photographs and micro-photographs the presence of collargol in the kidney substance. At operation two weeks after injection an infected area about 2 inches wide was found to be infiltrated with collargol and the capsule covering this area was lifted from the parenchyma by a layer of collargol. This mass extended down to the renal pelvis and was resected without going into the pelvis.

injection. These cases were under observation from one to three days before the catheterization, and each had a normal temperature. In Case VI the verified rectal temperature on the third day following the injection was 102.4° F., while on the fourth it was 104° F.

The urine of these cases before the injection was normal. Following it, it is not unusual to find white blood-cells and hyaline and granular casts which may persist for four or five days. Albumen is also present in definite amounts for varying lengths of time. Cases II and III showed small amounts when discharged and Case VI some eleven weeks after the injection. In the five cases operated upon, the presence of collargol was noted in the kidney or retroperitoneal tissues. In Case I there was an escape of approximately 15 cc. of dark brown fluid when the kidney was exposed, while in another a small amount was found in the peritoneal cavity. In Case VI the retroperitoneal abscess was undoubtedly caused by the presence of the collargol

kidney catheterized. Collargol was injected and an X-Ray picture taken. *Operation.*—May 29, upon exposing the left perirenal tissues, there was an immediate escape of approximately 15 cc. of dark brownish fluid, resembling collargol. The perirenal tissues were deeply stained a dark brown color. The kidney was normal in size. A small stab wound was made in the convex border and the pelvis explored. No evidence of stone or pus. A small rubber catheter was placed in the kidney. Patient had acidosis from the second to the fifth day, and acute dilatation of the stomach on the tenth. She improved from this time on until the fourteenth day, when there was marked bleeding from the incision and nose, and hæmatomata formed at needle punctures where subcutaneous infusions were given. The patient became very much weakened and drowsy. Pulse became slightly weaker. She died on June 12. No autopsy was obtained. *Urine.**—May 26, many R. B. C., and W. B. C. No casts (catheterized specimen). May 30, almost pure blood. June 5, W. B. C., a few R. B. C., and fine and coarsely granular casts voided. June 8, the same as at the last examination. Acetone and diacetic acid, negative. Albumen positive in all tests. The course of a case described by Rössle⁴ is quite similar to the



CASE II.—Gyn. No. 19227. Both kidneys injected. Elevation of temperature began 8 hours after injection and continued for 9 days. No operation.

which was noted at the first operation five days after the injection. Associated with the discoloration of the perirenal and periureteral tissues there is definite edema of these structures. No urine was at any time noted in the retroperitoneal space, nor did the exudate have a urinary odor. Whether the collargol escaped from the renal system by osmosis or rupture of the kidney or ureter is not clear. Inasmuch as at operation the kidney cortex has been seen to be stained and the pad of perirenal fat been found evenly discolored by the collargol, the escape is thought to be due probably to osmosis. The renal pelvis and upper portion of the ureter were examined where it was possible, but no lesion was found.

Many of these cases occurred in a series which were injected for the purpose of studying the renal pelvis in nephroptosis.

All excepting Case No. I have been catheterized and injected by the author.

CASE I. Gyn. No. 18414. Age 33. White.
Complaint.—Pain in the left side of back and left abdomen; painful urination. May 28, patient was cystoscoped and the left

one just mentioned. The hemorrhagic diathesis is especially interesting. The kidney was injected with collargol previous to operation. On the 8th day after operation the patient developed a sever hemorrhagic diathesis with parenchymatous bleeding in stomach, rectum and lungs. No cause for this condition is known, but is thought to be due to local renal injury caused by the injection of collargol and subsequent sudden absorption of the pure silver salt. At autopsy the tubules were filled with collargol which was pressed under the kidney capsule. Some of the tubules were seen to be broken. The renal area was edematous. In the liver, areas of necrosis were noted which were quite similar to those found in beginning eclampsia.

Rosenblatt and Margandies⁵ (Odessa), at the Congress of the *Deutschen Röntgen-Gesellschaft*, March 29, 1913, demonstrated the kidneys and ureters of a patient who died following the injection of collargol for diagnostic purposes. No rupture was seen in the specimen.

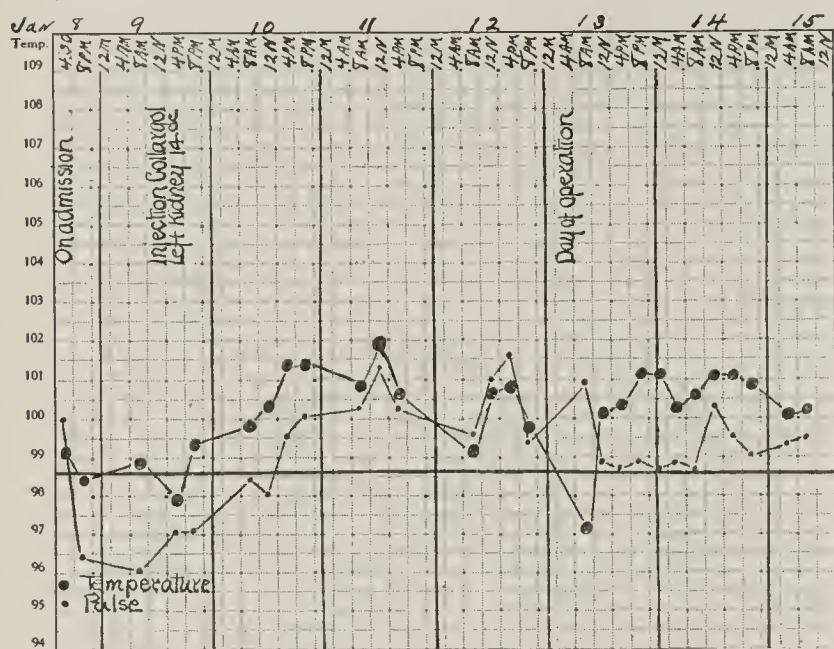
* The tests for sugar in the urine of the cases here reported were negative.

No mention is made of the method of injection used in these cases.

Prof. Rovsing (Copenhagen) does not use collargol in his cystoscopic work, preferring to make his diagnoses by other means. (Personal communication.)

CASE II. Gyn. No. 19227. Age 18. White.

Complaint.—Pain in right side of abdomen. April 11, both kidneys catheterized. 6 cc. of collargol injected into the right pelvis and 11 cc. into the left. X-Ray picture taken. Following the examination, the patient had quite severe pain in each side which lasted until the second day. Temperature eight hours after injection, 100.2° F. No operation. *Urine.*—Both kidneys the same. Sp. gr. 1004. Albumen absent. A few epithelial cells. April 13, patient has a "soreness" in each hypochondrium. Temperature 102.6° F. *Urine:* Catheterized specimen.—April 14, sp. gr. 1015. Albumen present. Reddish yellow sediment and masses of R. B. C., and a few W. B. C. Granular and hyaline casts. Considerable tenderness in left hypochondrium. Temperature 102.8° F. W. B. C., 8120. April 15, sp. gr. 1010. Albumen present; also R. B. C. and W. B. C. No casts. Condition improved. Temperature still



CASE IV.—Gyn. No. 18978. Left kidney injected. Temperature elevated 8 hours after injection. 102° F. on 3d day.

elevated. Patient remained in the hospital for ten days longer when she was discharged feeling quite well. Wassermann test negative. Calmette tuberculin tests, 1 per cent and 5 per cent, negative. When patient left the hospital, there was a slight trace of albumen, and some blood cells noted as present in the urine.

CASE III. Gyn. No. 19121. Age 30. White.

Complaint.—Pain in right side under costal margin. March 3, right kidney is in descensus, the upper pole being quite readily palpable. The ureters were catheterized, the urine from each side being negative. 21 cc. of collargol were injected into the right renal pelvis and an X-Ray picture taken. After the injection a catheterized specimen of urine from the right kidney showed some albumen, no casts, and a few red and white blood cells. *Operation.*—March 6, suspension of the right kidney. The kidney was slightly stained a deep brownish color. There was also a slight discoloration of the perirenal fat. Convalescence uninterrupted. A positive amount of albumen was found in the urine after the operation, which amount was present upon discharge, March 27. Both specimens were voided. No casts.

CASE IV. Gyn. No. 18978. Age 45. White.

Complaint.—Pain in left half of abdomen. Left kidney was movable, slightly tender and lower half palpable. January 9,

ureters were catheterized and 14 cc. of collargol was injected into the left renal pelvis. The urine from each kidney was normal. There was marked elevation of temperature three days following the injection. *Operation.*—Fourth day after injection, January 13. Suspension of left kidney. The kidney and perirenal fat at the operation were found to be deeply injected, these tissues having a deep brown color. There was a small amount of serous material, stained the same color, about the kidney. A small sinus which drained the perirenal area persisted at the lower angle of the incision until the end of the third week. Patient was discharged February 12, well.

CASE V. Gyn. No. 19142. Age 33. White.

Complaint.—Dull aching pain under right costal margin and in right lower back. Right kidney quite movable and in descensus. It can be depressed to the anterosuperior spine and to the median line. Left kidney normal. March 11, 30 cc. of collargol were injected into the right kidney and an X-Ray made. Patient had quite severe pain for six hours following injection. March 12, urine, clear. *Operation.*—March 12, suspension of the kidney. Appendectomy. There was a small amount of dark colored material (collargol) in the perirenal tissues. The pelvis was large and boggy but the kidney was normal in size and outline. The kidney and perirenal tissues were seen to be stained a deep brownish color. There was a small amount (approximately 2 cc.) of black fluid in the peritoneal cavity. *Urine.*—March 13, albumen present; many W. B. C. and R. B. C., and fine and coarsely granular and hyaline casts. Convalescence uninterrupted. This case is of interest because collargol-like material was found in the peritoneal cavity.

CASE VI.* Gyn. No. 19249. Age 32. Black.

Complaint.—Pain in right abdomen. April 21, right kidney catheterized. 10 cc. of collargol injected and an X-Ray picture taken. April 22, patient had nausea and vomiting yesterday and to-day. April 24, patient is fairly comfortable but has some pain in the lower right abdominal quadrant. No muscle rigidity. Temperature continues elevated since last night, 102.5° F. W. B. C. 16,800. April 25, continues practically the same. W. B. C., 21,200. Temperature 104° F. *Operation.*—April 26, both tubes and the appendix removed. There was a mild chronic pelvic inflammatory disease. The abdomen was opened through a median line incision. There was marked discoloration (a deep brownish and in parts blackish) noted throughout the right half of the pelvis and abdomen, extending to the lower pole of the kidney. This discoloration was entirely retroperitoneal. The adherent appendix was removed. A drain was placed through the cul-de-sac. Patient had a continued elevation of temperature, for the most part between 102° and 103° F. and at one time 105° F. This condition continued for 12 days after the operation when the temperature fell, remaining for a week at about 100° F. During the next ten days there were daily elevations of temperature, varying from 100° to 103.8° F. Suspecting the discoloration of the retroperitoneal tissues to be the cause of this disturbance, an incision was made in the right flank. There was an immediate escape of about 2ozs. of thick yellowish pus which contained definite fecal material. Digital exploration was carefully made to make sure no further pockets existed and a drain was placed in the incision. Fecal material was noticed on the dressings on the second day. The fistula persisted for 11 weeks. During the last three weeks of this period the fistulous tract was given a continuous irrigation of tap water five hours daily. In the week after the second operation the temperature remained between 102° F. and 104° F., but gradually fell. In the six weeks following there were numerous elevations to 103° F., twice to 105° F., and twice to 106° F. (All temperatures over 101° F. are rectal and over 103° F. are verified.) Widal

* A case quite similar is reported by Oehlecker in his interesting article. In our case a first radiogram was negative for stone.

and blood cultures negative. Haemoglobin 68 per cent. Fresh blood examination negative. On the 113th day after the first operation she was discharged well. *Urine*.—April 19th on admission, sp. gr. 1021. Albumen absent. Few W. B. C. No casts voided. April 22, sp. gr. 1020. Albumen absent. Cellular and hyaline casts. No R. B. C or W. B. C. (catheterized specimen). April 26, sp. gr. 1021. No albumen. Many hyaline and many fine granular and cellular casts. No R. B. C. (voided specimen). April 27, after operation, sp. gr. 1019. Slight trace of albumen. Many fine granular, cellular and hyaline casts. No W. B. C. or R. B. C. (catheterized specimen). There was a trace of albumen in all the examinations of the urine during the patient's stay in the hospital. There is no doubt but that the retroperitoneal necrosis and abscess in this case followed the widespread dissemination of collargol noticed at the first operation.

The unusual symptoms in these six cases, following injections of collargol, and especially the course of the last case seem worthy of record.

these symptoms, there are definite urinary changes. The examinations have shown W. B. C., R. B. C., with hyaline and granular casts to be present three days following the injection; casts for nine days; and albumen in two cases for 24 days; while in a third a trace was detected after 118 days.

In three cases where collargol was used, death has followed, but it is not evident that it was precipitated by the collargol.

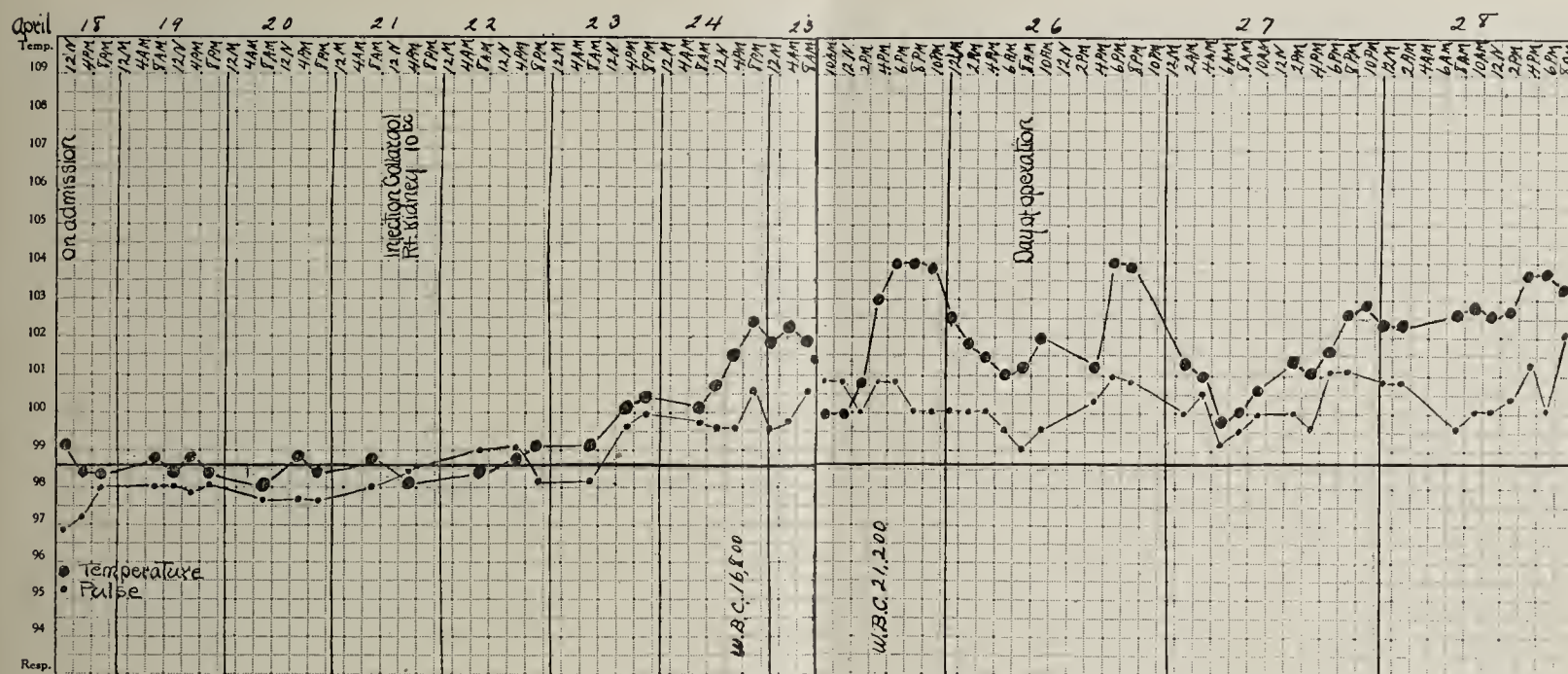
Collargol should be used only when absolutely necessary.

It should be allowed to run into the renal pelvis in small amounts and under very low pressure.

A freshly prepared solution, not over 15 per cent, should be used.

It is necessary that the symptoms here mentioned be known by those using this method of pyelography, and especial care be exercised to avoid their occurrence.

On account of the results here shown some other medium



CASE VI.—Gyn. No. 19249. Right kidney injected. Elevation of temperature began on 3d day following. 104° F. on 5th day. Retroperitoneal abscess.

Summary.—At operation, collargol has been found in the kidney and perirenal tissues in five of our cases, and in one case in the peritoneal cavity. The kidney and perirenal tissues in these cases were colored dark brown or bluish black and were edematous. The amount of discoloration was noticed in one instance to extend throughout the entire retroperitoneal space of the side injected. In this case a retroperitoneal abscess developed which necessitated a second operation.

The time between the injection and operation varied from one to five days.

Both 10 per cent and 15 per cent solutions were used. No difference in the resulting clinical symptoms was noted.

Pain may be quite severe, lasting for two or three days, and once for 10 days.

As shown by the charts there may be a definite rise in temperature, 102° F. being reported in two cases and 104° F. in another.

While no case of nephritis has been shown to accompany

must be sought which will give a shadow but not injure the renal substance. After a more extensive use of silver iodide emulsion, this material may be found to serve well.

During the past five months Prof. Kelly⁶ has been using it in pyelography and has found it quite satisfactory.

In conclusion, I wish to express my thanks to Prof. Kelly for his suggestions in this work and the privilege of reporting these cases. I am also indebted to Prof. Rovsing for his suggestions and the references sent me.

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KOPLIK'S SPOTS OCCURRING ON THE TONSILS OF A CHILD SUBSEQUENTLY FOUND TO BE ANAPHYLACTIC TO EGG-ALBUMEN.*

By SYDNEY R. MILLER, M. D., Baltimore, Md.

The following case is reported for two reasons: First, because of the unusual and misleading symptoms at the onset, and second, for the reason that it presented, it is thought, characteristic Koplik's spots in a manner hitherto not described.

Present Illness.—On the evening of March 29, 1913, I was hastily summoned to a neighbor's home by a telephone message, saying, "The baby is choking to death." I found the child, a girl of ten months, seated on its mother's lap, very cyanotic, breathing rapidly, and with a to-and-fro stridor that was audible as soon as one entered the door of the house. This condition had come on without warning within the space of about ten minutes, and while in the mother's arms; she was positive that the child had swallowed nothing. For some three or four days the baby had been unusually restless, fretful and hard to feed, symptoms attributed by the mother to teething. There had been no cough, coryza, or conjunctivitis. The baby was a full-term infant of normal delivery and breast-fed.

Physical Examination.—Temperature, 104.5° F. Pulse, 160. Respiration, 60 to 70. The eyes and ears were quite negative. So far as could be determined the lungs were clear on percussion and auscultation. Aside from its rapidity, the heart seemed normal in size and action. The skin was clear, hot, and dry.

The most interesting finding was in the throat, which was examined with the aid of a pocket electric light equipped with a Tungsten bulb, which furnishes a white light. The entire buccal and pharyngeal cavity was of an intense dusky red color; no Koplik's spots were to be seen on the lips or cheeks; the uvula was swollen. There was not the slightest evidence of a membrane in the throat. The tonsils, however, were remarkably swollen and succulent, nearly touching each other in the mid-line when the child gagged; on each tonsil there were visible some 25 or more small bluish, semitransparent, elevated bodies, averaging considerably less than the size of the head of an ordinary pin; three were visible on the anterior pillar on one side; the majority of them showed a minute white dot in the center of the otherwise bluish-gray structure. The appearance was that of minute vesicles, peppered over a diffusely red base. The structures in no way suggested a follicular tonsillitis; indeed, I had no notion of, nor time to speculate, concerning their identity. Smears, made while the child was gagging, subsequently showed no Klebs-Loeffler bacilli, nor were the spots described above in any way perceptibly damaged in the process of swabbing the throat.

The child was with difficulty given an effectual enema, following which her feet were placed in a hot mustard bath, and a steam kettle was started in the immediate vicinity. Attempts to induce vomiting were ineffectual. About half an hour after

starting the foot-bath, or about one hour from the time of onset, there was decided improvement: the respirations had fallen to 35 or 40, the stridor was less marked, the pulse slower. Simultaneously with the relief of symptoms there occurred, first on the forehead and face, a dusky, reddish mottling, and, almost as one watched it, this eruption became more and more outspoken, so that within three hours from the time of invasion, the child, now absolutely free from respiratory distress, was literally covered from head to toe with a rash characteristic of measles. Exhausted, the baby fell into a deep sleep.

The next morning the temperature was 103.5° F. The face was distinctly swollen and the conjunctivæ quite red. The rash was outspoken, hyperemic, and easily palpable under the skin. There now was a cough, and definite signs of a bronchitis over the right chest. Examination of the mouth again showed a total absence of Koplik's spots on the cheeks or lips; the elevations on the tonsils were somewhat larger and whiter in the centers, though each one remained discrete. By the following day these spots had practically disappeared; that is, within 48 hours from the time of onset, the tonsils, meanwhile, having subsided to a nearly normal size and appearance. By evening of the third day the temperature had fallen to 99° F., and the rash had commenced to fade, though leaving behind it a rusty discoloration of the skin, still visible two weeks after the onset. There was slight, but definite, desquamation associated with pruritus. The child made an uneventful recovery.

Exactly two weeks prior to the sudden attack above described, the baby's sister, four years of age and also my patient, had come down with measles. She had had three days of prodromal sneezing and coryza, and some conjunctivitis, before I saw her; during those days the two children had played together and slept in the same room. The sister had a severe attack of measles, complicated by an otitis media. There were other cases of measles in the neighborhood, and a serious epidemic was prevalent in Baltimore. These facts, taken in conjunction with the clinical course of the disease, fully justified, it is thought, the diagnosis of measles, and the opinion is advanced that the eruption seen on the tonsils was an aggregation of characteristic Koplik's spots in an unusual location.

The typical enanthem of measles, first adequately studied by Henry Koplik,¹ of New York, in 1896, is described by him as follows:

On the mucous membrane lining the cheeks and lips we see a distinct and pathognomonic eruption. This consists of small irregular spots of a bright red color; in the center of each spot is the interesting sign to which I wish to call attention. In strong daylight we see a most minute bluish-white speck. These minute bluish-white specks in the center of a reddish spot are absolutely pathognomonic of beginning measles. I have never met them elsewhere, and when once seen they are a certain forerunner of the skin exanthema. These bluish-white specks are sometimes so delicate that they can be seen only in a strong window light. No

* Read before the Johns Hopkins Hospital Medical Society, May 5, 1913.

one has ever called attention to these bluish-white specks as a forerunner of the skin eruption. Their background is the irregular red spots referred to above. They cannot be mistaken for sprue, for they are not so deeply white, nor are they as large as sprue spots, and sometimes we must, as I said, look sharply and evert the mucous membrane of the cheeks to find them. These bluish-white specks surrounded by a red area are found, as I said, on the mucous membrane of the cheeks and lips and not on the soft or hard palate. Sometimes only a few red spots exist with their central bluish points, a dozen or more, and again these whitish specks may cover the whole lining membrane of the cheeks and lips. If these bluish-white specks on a spotted background are at the height of their development, they never become as white and opaque as sprue spots, and therefore can be easily differentiated after having been once seen. Nor do they ever coalesce to become plaque-like in form. They always retain their punctate character. If the mouth has been washed these spots may have been rubbed off, and then the appearance is lost.

As the exanthema on the skin appears and spreads, the eruption on the mucous membrane inside of the cheeks and lips becomes diffuse and the characters of a discrete eruption or spotting disappear, and we have an intense general redness which is simply dusted over with myriads of these bluish-white specks. This being so, it will be seen that this eruption of bluish-white specks on a spotted or red background is of the greatest value at the very outset of the disease, before the appearance of the eruption; also at the beginning and height of the skin eruption. When the skin eruption or exanthema is at its efflorescence, the buccal eruption begins to fade and gradually disappears, even while the exanthema is still out. In the later stages of the fading skin eruption the phenomena described above are no longer seen.

In a personal communication Dr. Koplik states: "The measles enanthem, when at its height, can be seen on the buccal mucous membrane, the lips, fauces, roof of the mouth, conjunctivæ, and larynx; Koplik's spots never appear as you describe them." Dr. Howland states that he has never seen the spots on the tonsils; and Dr. von Pirquet, to whom I told my experience, gave me a similar answer. In a fairly exhaustive search through the literature, it has been thus far impossible to discover the mention of any analogous case, though Koplik's spots are described in nearly every other locality, including the intestines. It was suggested by Dr. Koplik that the case was possibly one of Rötheln, or German measles, in which the "Röthelntasche" of Forscheimer and Thomas² was seen. This is tersely described as consisting of "minute, bright, rosy-red points, seen on the uvula and soft palate, rarely on the hard; it is present only in the first 24 hours." "They resemble Koplik's spots very much, but fail on close study to show the minute bluish-white speck." * This latter feature was prominent, however, in this case. German measles has not been prevalent hereabouts. The rash was typically that of measles, and accompanied by constitutional disturbances certainly more severe than is met with in Rötheln. The rash, moreover, left a slowly fading discoloration; there was no adenitis and the child had been exposed to measles. These features make the diagnosis of Rötheln certainly remote. That the elevations were not merely projections of swollen tonsillar crypts was manifest by their rather close grouping, translucent appearance, small size, evanescent existence and the presence

of several on one pillar. There is the possibility that the case was one of undoubted measles, showing at the onset herpes simplex, localized on the tonsils. Facial herpes in measles is not uncommon, appearing generally at the same time as the eruption, or a little earlier. The same is true of herpes zoster; neither one causes "any noticeable variation to the usual course of measles." It is, therefore, quite conceivable that a true angina herpetica might occur, but the lesions did not run through the usual herpes cycle; they never coalesced, they were never closely enough packed together, little ulcers did not form, nor did the vesicles become more and more milky white during the short period of their existence. Sprue was absolutely ruled out. In view of these facts, it seems not unreasonable to conclude that in a case subsequently running the typical course of measles, true Koplik spots occurred on and were curiously confined to the tonsils, preceding the rash and disappearing within two days after its appearance.

Other interesting and uncommon features in the case were these: First, the unusually acute onset with signs of laryngeal obstruction. Laryngeal diphtheria, foreign bodies, acute œdema of the glottis and mediastinal conditions called for consideration. All of these conditions were ruled out by the rapid disappearance of the laryngeal symptoms, which were doubtless due to a combination of acute catarrh and spasm of the glottis. Rolly,³ in a series of 800 cases of measles, observed severe initial laryngeal symptoms in only seven instances, in patients varying in age from eight months to three years; in all the symptoms followed the appearance of the rash. Huebner⁴ states that the disease may commence with unusual severity, particularly in very young children: "The laryngeal submucosa may be so greatly swollen that serious symptoms of pseudo-croup may usher in the disease." Still,⁵ in discussing "Laryngitis stridulosa," in his admirable book on "Common Disorders of Childhood," says: "A practical point to be remembered in diagnosis when a child becomes hoarse and stridulous, and has a high temperature, is the occurrence of the symptoms as part of the invasion of measles. I have repeatedly seen this acute laryngitis of measles mistaken either for ordinary catarrhal laryngitis or for diphtheria, and have seen tracheotomy done—whereas the appearance of the rash, 24 hours later, showed that the symptoms were due to the pre-measles laryngitis. The stridor and obstruction to respiration in these cases usually subsides as soon as the rash appears." It would seem, however, that a laryngitis, developing with this alarming rapidity and followed so soon by the eruption, is quite unique. That such an event may occur is a matter of considerable diagnostic importance, especially during an epidemic of measles.

No less striking was the sudden subsidence of respiratory distress synchronous with the initial appearance of the rash, and the almost perceptible spread of the eruption, involving the entire body, in a matter of about three hours. Holt⁶ states that the entire body may be covered in a few hours, while most other writers are content in stating that in certain cases the rash may spread with unusual rapidity. Dr. von Pirquet, in his recent exhaustive monograph on the skin manifestations

* Dr. Koplik.

of measles, makes the italicized statement that "a complete development of the enanthem inside of a single day speaks against measles." Yet, even if his ingenious hypothesis of progressive intracapillary agglutination of the causative agents of measles by specific anti-bodies, advanced to explain the nature, initial location and subsequent spread of the enanthem, be true, one may still conceive of a sudden, explosive-like dissemination of agglutinins and rapid fixation of antigen throughout the entire body, manifested, as in this case, by speedy and complete development of the eruption.

Finally, experience in this case strengthens the widely prevalent idea that a hot bath, given to "bring out the rash," has a decided beneficial effect. Certainly, the result here was most remarkable, though mere coincidence cannot be ruled out. Heubner, in speaking of cases with severe laryngeal symptoms, states: "They are effectually influenced by a suitable anti-phlogistic therapy."

It is hoped that verification of these unusual findings may ultimately be forthcoming, or that errors in diagnosis, not patent to the author, may be revealed.

On the day prior to that on which this report was read, it was accidentally discovered that the child in question was markedly anaphylactic to egg-albumen; this was made manifest by alarming laryngeal distress, fever of 103° F., and the rapid development of an urticarial rash that literally made the child's features unrecognizable. These symptoms came on within about a half hour after feeding the child some egg-white and orange juice, and quickly subsided under treatment precisely the same as that used at the onset of the attack of measles. Though the tonsils were swollen, there was not the slightest evidence of an eruption upon them or any other part of the buccal cavity. Similar negative findings occurred during a subsequent milder anaphylactic reaction, purposely induced.

As a result of questioning, it developed that on the very evening of the day on which the child's illness commenced it had been given egg-white for the first time, so far as is known, in its life, a detail which quite naturally had never entered the mother's mind as being in any way associated with the severe symptoms described. While there exists no reasonable doubt

as to the genuineness of the attack of measles, the egg-white anaphylaxis introduces a new factor which makes it quite impossible to say to just what the alarming manifestations at the onset were wholly due. The entire illness may have been measles alone, in an intense form, as was thought; on the other hand, despite the apparent lack of previous sensitization, anaphylactic phenomena, by a curious coincidence may have ushered in, and considerably hastened the clinical manifestations of measles. In any event, it seems unlikely that anaphylaxis had any share in causing the tonsillar eruption thought to be that of Koplik's spots.

A von Pirquet test performed with egg-white and suitable controls induced a speedy and marked local reaction associated with a mild constitutional disturbance. It was subsequently found that a constitutional reaction followed the administration of one teaspoonful of a mixture composed of one pint of water plus one drop of egg-white; a like amount of albumen diluted with one quart of water was tolerated perfectly. No anaphylaxis resulted from the administration of yolk alone. Commencing with the dilution which failed to produce a reaction, the child was given gradually increasing amounts of solutions of increasing strength. The dosage was always one teaspoonful given three times during the day; the result has been that, in a period of about three months, the child has been desensitized to such an extent that one dram of pure egg-white is now taken with impunity and the von Pirquet test remains as negative as are the controls.

I wish to express my appreciation for opinions given me by Dr. Koplik of New York, and Dr. von Pirquet, formerly of Baltimore; and to thank Dr. Howland, of this clinic, for his kindly criticism of this report.

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A BRIEF HISTORY OF QUARANTINE.*

By W. W. FORD, M. D.,

Associate Professor of Hygiene and Bacteriology, The Johns Hopkins University.

Although the first enactment for the delay and isolation of travelers was adopted in the 15th year of the reign of the Emperor Justinian, A. D. 542, and a sort of detention had been known and practiced in the Orient since the 7th century, quarantine in the modern sense may be said to have originated in Italy in the 13th century as a result of the invasions of plague from the Levant into Europe. How frequent these

invasions were is indicated by the fact that from 900 to 1500 A. D. plague appeared in Europe sixty-five times with dreadful ravages and terrific loss of life. The fear inspired by these visitations led the Italian cities, then the centers of trade between Europe and the Orient and dependent upon this commerce for their prosperity, to begin the enforcement of drastic regulations at their ports to prevent the importation of the dread disease by the incoming vessels. Venice appointed three commissioners of health in the year 1384, the

* Read May 16, 1913, before the Medico-Chirurgical Faculty of Maryland.

first year of the Black Death, increasing the number to six in the next century. Her example was followed by Florence the same year, by Reggio in Modena in 1374, by Lombardy in 1374, and by Milan in 1399. Maritime quarantine started in 1403 in Venice with the establishment of a detention hospital on an island adjoining the city for the isolation of all travelers from the Levant for a period of 40 days. For this purpose an old almshouse, known as the House of St. Lazarus, was employed and from this usage came our modern term lazaret or lazaretto. Genoa followed the example of Venice in 1467 in establishing a lazaretto and in 1476 the old leper hospital of Marseilles, then almost empty as a result of the dying out of leprosy, was converted into a plague hospital. It is worthy of note that whereas the earliest quarantine was directed against plague the isolation of individuals inflicted with certain diseases was by no means a new idea. The isolation of lepers was a well established practice at this time, its origin dating from the remotest periods of the world's history. About the year 1490, or probably a few years later, if we accept Ivan Block's view that syphilis was brought back by the sailors returning with Columbus on his second voyage to the new world, an ineffectual effort was also made to check the invasion of lues into Northern Europe.

In the year 1526 the greatest lazaret of early times was erected in Marseilles on the island of Pomègue adjoining the city, and here the most rigid and strict quarantine of the old world was set up. Later sanitary regulations for the whole of France were issued by Colbert, minister to Louis XIV, on August 25, 1683, and the Board of Health of Marseilles was given almost absolute power.

In 1485 Venice had adopted the rule that all vessels coming from infected ports must be detained for a period of 40 days during which time they must lie in harbor without intercourse with land or other vessels. After this period they could discharge goods or passengers. The simpler remedy of sending ships back to their port of departure was manifestly injurious to trade and the practice of permitting them to land after the 40 days detention was clearly a concession to the interests of commerce. The important relation of quarantine to commerce, so much emphasized by the English authorities, was thus clearly recognized from the first. While Venice was the pioneer in the establishment of quarantine systems, it was in Marseilles that the model quarantine station of the old world developed, one far more important, indeed, than that in Venice. According to Fischer¹ all incoming vessels here had to be provided with a health pass (bill of health) or *patent* which was to be filled out by a trusted official of the port of entry at the port of departure. On this pass must be stated what the condition of health might be in the countries and cities from which the ships came and which they touched on the voyage. Patents were of 4 kinds:

1. *Patente nette*, when the health of the port of departure was entirely satisfactory.
2. *Patente touchée*, when ships came from infected ports but no cases of illness existed there at the time of departure.

3. *Patente soupçonnée*, when a malignant epidemic prevailed at the port of departure or caravans had arrived there from pest neighborhoods.

4. *Patente brute*, when the plague was present in the port of departure and the ship had wares from an infected port on board.

In addition to the possession of proper patents, the ships themselves, their passengers and crew, and the goods they carried were subject to careful examination. The wares on board were divided into two classes, susceptible and non-susceptible, and all cases of illness and all deaths during the voyage had to be reported. Finally a classification was adopted for the Oriental ports from which the vessels came, which had great influence upon the severity of the regulations enforced. Völkers² states that ships with a *patente nette*, non-suspicious wares and from harbors where conditions of health were satisfactory, Class I, were detained 18 days. Ships with the same conditions but from harbors which had been infected but showed no cases of illness at the time of departure, Class II, were detained 25 days. Ships from harbors where plague might be epidemic or where caravans had arrived from pest neighborhoods, such as Smyrna or Constantinople, Class III, were detained 40 days in quarantine after a previous exposure of all wares to the air for three weeks. Finally if cases of illness were on board, the passengers were detained 80 days and the goods 100 days. On each side of the ship a row of planks was removed to permit aeration of the ship's contents. If any patient with plague recovered he had to undergo a new 80 day quarantine after complete healing of the buboes. Whenever a patient died or a new case of the disease appeared the goods on board were subjected to a new quarantine, but after a third appearance of plague the ship and all its contents were burned. At the quarantine station a lazaret was established for the reception of the sick, the well and the suspects. These strict rules caused naturally great loss of time and money and worked great injury to commerce. They were indeed so difficult to carry out that later quarantine ships were substituted for the lazarettos so that the regulations could be better enforced.

The quarantine system founded upon the 40 days detention first established by Venice remained in force in the Mediterranean up to modern times, Austria, France and Italy adhering to the original scheme. The measures were directed solely against plague, and with the dying out or at least partial disappearance of the Black Death from the civilized world, quarantine regulations began to lose their rigidity. With the appearance of yellow fever in Spain in the beginning of the 19th century and the arrival of cholera in Europe in 1831 there was a revival of interest and a demand for somewhat more stringent precautions than were then in force. Cholera and yellow fever were added to the list of quarantinable diseases and in 1831 new lazarets were established in Europe, notably in Bordeaux, where a very extensive plant was set up which was afterwards devoted to another purpose. The development of the old-fashioned system of quarantine

in the 19th century reached its maximum possibly in Spain and Portugal where special regulations were carried out to prevent the entrance of yellow fever from the New World. Here we see the transfer of the center against which nations quarantined from the Levant to South America. The largest lazarette in the world was established at Lisbon, on a hill opposite the Belem tower, 4 miles from the city, at a cost of \$1,000,000 to the Portuguese government. It consisted of seven pavilions arranged in a semicircle with the convexity towards the river. It was under the Department of the Interior which managed it at a loss and let out the contract of feeding and housing the passengers to the lowest bidder. At this station quarantine was imposed on all ships, passengers, and cargoes coming from Brazil, the time varying from 5-7 days according to whether the Brazilian port was infected or suspected. A bill of health was issued to the captain of the vessel by the Portuguese consul at the port of departure giving the number of deaths from yellow fever during the past 8-10 days. Quarantine could be lifted when an absolutely clean bill of health was presented, which, however, rarely happened in the old days, since yellow fever was endemic in most cities in Brazil up to the end of the 19th century. During December, January and February the baggage and cargo of incoming vessels only were subject to detention on the theory that the virus of yellow fever could not develop at Lisbon, the passengers being permitted to go on shore at once with their hand luggage. For the rest of the year all passengers from Brazil were sent to the lazaret to remain there the allotted time, their effects being aired and fumigated or disinfected. Certain articles, including cotton, hair, hemp, letters, parcels, hides, fresh meat, wool, linen, skin, feathers, and silk were regarded as susceptible. All these were fumigated with chloride of lime, and the inside of the ship was washed with chloride of lime or other disinfectants. This rigorous quarantine was a concession to popular opinion, since a terrible epidemic of yellow fever broke out in Lisbon in 1857, with 19,000 cases and 6,000 deaths, traced to a tainted ship and cargo from Rio. The quarantine practiced at Lisbon was copied faithfully at the Azores, at Madeira and the Cape Verde Islands. The old quarantine traditions were also maintained at two chief lazarets in Spain, one at Vigo on the Atlantic Ocean and another at Port Mahon on the Mediterranean Sea. These were known as "foul lazarets." Certain ports, as Havana in ordinary times, and all ports in cholera epidemics (i. e., when cases of cholera existed there) were known as "foul ports" and all vessels from such places were compelled to enter these stations for quarantine. Only a "quarantine of observation" lasting 3-6 days could be imposed at other ports.

Turkey and Greece likewise held to the old traditions of quarantine with lazarets at the Piræus and in the Dardanelles. The lazarets in various Mediterranean, Adriatic, and Levantine ports were also maintained, including Malta and Gibraltar where the machinery of the old-fashioned quarantine still exists and can be used in cholera times.

The classical rigid quarantine which had been in vogue throughout the entire world was gradually given up except in a few areas such as those mentioned, and by the year 1886 existed in but one or two places with its pristine rigor and severity. This was due to several factors chief among which may be placed the influence of England and the growth of the modern sciences of bacteriology and protozoölogy. As early as 1815 England abolished quarantine, directing her efforts towards an improvement of the sanitary conditions of her ports and substituting the system of revision or inspection. This system took definite form in an order of the Local Government Board in 1873 according to which no vessel was detained or refused *pratique* unless there was a communicable form of sickness on board or had been during the passage. It was the duty of the officers of custom to question the captain as to any cases of contagious disease among the ship's company or the passengers. If such existed, report was made to the local sanitary officers who inspected the vessel, detaining all on board till the inspection was made, the sick removed to the hospital and disinfectants applied. This principle was accepted by the Sanitary Conference in Vienna in 1874, and was adopted by all European maritime states except Spain and Portugal.

As early as 1847 France created six medical posts in the Orient at Constantinople, Smyrna, Beyrouth, Alexandria, Cairo, and Damascus, the officers at these cities having the especial duty of keeping their government informed of the sanitary conditions there. The work of these French sanitarians was really the occasion of the first sanitary conference held in Paris in 1851. This was further necessitated by the growth of commerce between countries and the difficulties encountered in the application of the principles of the quarantine of detention. It has been followed by a number of other conferences which, in the main, have not led to as great an improvement and advance as was to be expected. Changes in quarantine laws looking toward simplicity and effectiveness of operation have come not as the result of international change of opinion, but as the result of friction between powers in enforcing quarantine regulations at a time of threatening epidemics. The first international sanitary congress was held in Paris in 1851, eleven powers sending delegates, Austria, Great Britain, the Roman States, Sardinia, Sicily, Spain, Greece, Portugal, Russia, Tuscany, and Turkey. A code was prepared for uniform action, but only France, Portugal and Sardinia were willing to sign it.³ Another conference was held in Paris in 1859, a third in Constantinople in 1866, and a fourth in Vienna in 1874. At this last the new principle of inspection advanced by the English sanitarians was adopted. According to this principle all vessels were to be examined at the port of entry to determine the presence of disease. Sick individuals only were to be detained, the well allowed to continue their journey. This change in system was regarded as necessary in view of the enormous commerce and travel extending over the entire world. It was evident that quarantine stations to provide for all

passengers and goods regardless of the point from which they came would either be of enormous expense and a great burden in order to be effective or the detention would develop into a mere formality. Added to this was the danger that the quarantine stations themselves would become foci of infection. In 1892 a conference was held in Venice which resulted in the production of a sanitary code which was adopted by the European nations. According to this a ship should be judged not merely from its port of departure, but according to the length of time which had elapsed since departure and from the presence on it of cases of illness, which condition should be established by medical inspection. Vessels were divided into three groups. Clean (*indemne*) vessels were such as had had no cases of disease at the time of departure or during the voyage. Suspected (*suspect*) vessels were those in which cases had occurred, but not within the past few days before debarkation, the free period between the last case and the day of arrival being longer than the incubation period of the disease in question. Infected (*infect*) vessels were such as had cases on board at the time of arrival or had had such during the past few days so that the incubation time of the disease had not passed between the last case and the time of arrival, the possibility thus remaining that latent cases or cases in the incubation period might still be present. This conference had little influence in promoting the adoption of uniform regulations by different countries except from the theoretical standpoint. But the same year a cholera epidemic arose at Hamburg which showed that many of the old quarantine regulations were absurd, the greatest injury being done German commerce by injurious disinfection of wares. As a result an International Congress was held in Dresden in 1893 which established common rules for handling ships in cholera epidemics. The Dresden meeting dealt only with cholera and the measures to be adopted on land and along international borders. It first brought out the necessity of an international notification of the appearance of quarantinable diseases in epidemic form or as single cases. At this conference also a new principle was adopted in regard to passengers, permitting a medical control and observation of those unsuspected of infection, without restraining their movements or retaining them in any one particular place such as the quarantine station. This is manifestly difficult of application. In 1894 bubonic plague, which for years had lain dormant and seemed indeed to have disappeared from the world, again made its appearance in Asia and in 1896 raged in Bombay. The following year it threatened Europe causing the greatest uneasiness. It is remarkable how quickly the world went back to the primitive conditions of the quarantine of the Middle Ages. In Sicily and in Malta ships from India were kept out of port by cannon shot and in Marseilles such vessels were compelled to leave the docks. The danger to Europe from plague led to another international sanitary conference which met in Venice on February 16, 1897. This took cognizance of the new knowledge about pest and completed the regulations in regard to this disease corresponding to those prescribed for

cholera. The incubation period for cholera was fixed at five days and that for plague at eleven days. On March 19th a series of agreements was published which were in the main adopted and which the Paris Convention of 1903 (the last) ratified and followed. At this conference 20 powers signed the international agreement for uniform quarantine rules and administration.

SANITARY CORDON.

At various times in the history of the world a cordon of troops has been employed to prevent the passage of individuals from infected to non-infected districts. In 1743 pest became epidemic in the state of Messina and the Viceroy ordered out a double cordon of troops to isolate the city of Messina from the rest of the island. The two cordons ran parallel, the outer consisting of 2610 men and the inner of 1089. All provinces of Sicily which were outside the cordon remained pest-free. A similar cordon was established by Russia in 1830 when the Kaiserhof in St. Petersburg protected itself against the encroaching cholera by a cordon of troops and later the same measures were adopted by Prussia to keep cholera from entering from Russia, a cordon of troops being stretched along the entire Russo-Prussian border. Still later in 1878 a Russian colony on the river Volga named Wetljankaja, with 1700 inhabitants, got Oriental plague which soon extended to the neighboring villages. A military cordon was set up surrounding the entire infected area. The inhabitants of Wetljankaja were removed, their property appraised, the citizens reimbursed and the village burned. An additional cordon was also placed around Zarizin, a neighboring commercial city of importance and the terminus of the Russian Railway system. These various cordons were maintained several months until the plague died out.

In 1884 the *cordon militaire or sanitaire* was set up by Italy against France in the passes of the Pyrenees, another the following year being established by Portugal against Spain. The American variety of this *cordon sanitaire* is familiarly known as the "shot-gun quarantine" which has been resorted to with great frequency in the past and not so very remotely. The last shot-gun quarantine was seen in this country during the time of the great expansion of small-pox after the Spanish-American war.

MODERN QUARANTINE.

According to Gotschlich⁴ the principles of modern quarantine are as follows:

1. Obligatory notification of epidemics between powers, the reports being sent by telegram or cable and later, at greater length, by letter. This full reporting is not simply for the benefit of other nations, but is primarily for the benefit of infected ports since the sooner other ports are satisfied that all necessary regulations are carried out the sooner will any unnecessary or inconvenient restrictions to commerce be done away with. An unsatisfactory or untrue report on the part of any country will awaken mistrust and lack of confidence on

the part of other countries and greater difficulty will be encountered in the lifting of embargo.

2. Quarantine regulations are not applied to the entire country but only to the area where the epidemic exists (*circonscription territoriale contaminée*). An infected area is that point where cases of disease appear. Ten days after the last case is diagnosed, provided proper precautions be carried out, the area in question is again opened to free and unrestricted commerce. All vessels which have left an infected port five days before the breaking out of disease are to be regarded as free from suspicion.

3. Preventive measures must be carried out before the departure of the ship from an infected port and during the voyage. Passengers and crew must be supervised by medical authorities before departure, individuals with suspicious symptoms being left behind. Dirty clothing and objects of personal nature must be disinfected before departure. This usually may be limited to passengers of the third class and to the ship's company, since it has been shown that, in general, individuals belonging to the better walks of life seldom carry diseases like cholera or plague. Ships must be cleaned and provided with drinking water from an uninfected and unsuspecting source before leaving port.

4. During the trip careful medical inspection of all individuals on board must be carried out and proper disinfection applied when suspicious cases occur. For certain classes of vessels, particularly pilgrim ships and emigrant ships, a ship's doctor and an apparatus for steam disinfection are obligatory provisions.

5. Measures in the port of entry depend upon the results of the medical examination of incoming vessels. Unsuspected or unsuspecting ships are allowed to go free at once after the doctor's visit (*libre pratique*) provided five to ten days have elapsed between the time of departure and time of arrival, five days for cholera and ten days for plague, the maximum incubation period. By shorter journeys this time is to be completed in quarantine. At the discretion of the quarantine officer all non-suspected ships may be treated as suspected. All articles on board such as old or dirty clothing and personal effects must be disinfected if the physician deems them likely to convey infection. Suspected ships must be inspected by the quarantine physician, all rooms occupied by cholera or plague patients must be disinfected together with all dirty clothing and personal effects. All bilge water, water ballast and drinking water must be discharged and a new supply obtained from an unsuspecting area. Passengers and ship's company must be kept under observation 5-10 days (depending on the disease), and during this time the landing of the crew is to be limited as far as possible. Passengers may be allowed to continue their way but must be kept under police supervision till the end of their journey. If the ships be actually infected by the occurrence of cases of disease on board the sick must be transferred to quarantine hospitals, and the dead bodies interred with all possible precautions and

all other persons kept under observation either at the quarantine station or at such places as they may select. This observation must last five days for cholera and ten days for plague.

WARES OR GOODS.

According to the Venice Conference the following materials are infectious (*marchandises susceptibles*): clothing and underclothing, rags, refuse, used garments, carpets, hangings, laces, hair, raw skins, animal wastes and unclean wool. For cholera certain articles of diet are also susceptible especially milk, butter, vegetables and fruits. The transposal of infectious material from an infected area is forbidden. The retention of wares in quarantine as formerly practiced is now given up, but all infectious material is to be at once disinfected without foolish formalities, such as the disinfection of letters. (The same rule would probably apply to money.)

QUARANTINE OF PILGRIMS.

The great danger to Europe which rose from the various bands of Mohammedan pilgrims to Mecca passing through the Suez Canal and the recognition of the part they had played in earlier times in the dissemination of disease led the Paris Conference of 1894 to establish special rules for these individuals as regards Asiatic cholera, and the Venice Congress of 1897 adopted similar rules for plague. According to these rulings all pilgrims are to be examined before departure from home and their effects disinfected. To accomplish this properly a limited number of ports are selected from which pilgrims are allowed to depart for Mecca, and individuals without money to defray the expenses of the trip are not permitted to leave. Pilgrim ships must always be provided with a doctor and an apparatus for steam disinfection. Overcrowding should be avoided, cleanliness insisted upon and a good supply of food arranged for. In addition to these general regulations applicable to pilgrims before departure, the Egyptian government now requires that each pilgrim from Egypt should have a pass with his correct name and address without which he cannot again land in Egypt. This is especially designed to prevent the return to Egypt of irresponsible vagabonds, wandering about from point to point, objects of charity and a danger to the community.

Pilgrim ships are detained in quarantine at a number of points. Vessels from the South are quarantined at Kameran (or Zameran) on the Arabian side of the Red Sea, 200 miles within the Straits of Bab-el-Mandeb. This station is under the control of the Turkish Government and has usually been regarded as hopelessly inadequate. Ships from the North are examined either at Wejh on the coast of Arabia, half way between Jedda and Suez or at El Tor on the Sinaitic side of the Gulf of Suez. The station at El Tor under the control of the Egyptian Government is entirely satisfactory. There 20,000 pilgrims can be cared for. The station lies on the west coast of the peninsula of Sinai on the land side, completely shut off from the adjoining desert by a high wire fence. Disembarkation is possible only by landing bridges, so that

the station is completely isolated. On landing the pilgrims are passed into the disinfection halls which are separated into clean and dirty sides. Here on the dirty side the pilgrims must completely disrobe, take a douche bath (what a trial for a pilgrim!) while their clothing and effects are disinfected. Transferred to the clean side the pilgrims are provided again with their disinfected clothing and divided up into detachments. These detachments are kept under observation for a period of time varying from three days, if no cases of plague or cholera existed at Hedjaz, the point from which they disembark, to eighteen days if cases of the disease did exist there. Should a case of disease break out in any section of the pilgrims, this section only must be quarantined again for eighteen days from the date of isolation of the last case.

The quarantine station at El Tor is directly under the authority of an Egyptian International Commission, *Consul sanitaire maritime et quarantenaire d'Égypte*, which also maintains a station for passenger ships at Moses' Wells on the Red Sea. Special regulations are enforced at these stations for all vessels which pass the Suez Canal. Every ship is subjected to medical inspection. Should sick cases occur they are transferred to isolation hospitals at the quarantine station and the parts of the ship contaminated by them disinfected. The other passengers and crew are either retained in quarantine if no doctor or apparatus for steam disinfection be on board or may remain in the vessel in the latter event. After five to ten days freedom from disease the ship is allowed to go through the Suez Canal (*transit en quarantaine*) but must not come in contact with the shores of the canal.

Quarantine stations for emigrants similar in character to those for pilgrims are now maintained at a number of ports, particularly in Germany. One of the most complete of these is that of the Hamburg American Line in Hamburg.

QUARANTINE IN THE UNITED STATES.

The first conference in the United States for a uniform system of quarantine regulations was one of Boards of Health in Philadelphia in 1856 occasioned by the presence of yellow fever in Bay Ridge the year before. Others followed in 1857 and in 1859 but nothing was accomplished in the way of adopting uniform regulations in this country, the various cities continuing to operate their own quarantine stations and enforce their own laws, until the passage by Congress of the Act of February 15, 1893, entitled "An Act Granting Additional Quarantine Powers and Imposing Additional Duties Upon the Marine Hospital Service." This act established a national system of quarantine designed primarily to supplement and assist the various local authorities in the establishment and enforcement of proper laws. Gradually the National Government through the Marine Hospital Service, now the Public Health Service, has assumed control of various quarantine stations in this country and at the present time is operating nearly all the important stations, including those on the Atlantic seaboard with the exception of New York, Boston and Baltimore. Up to 1881 the following diseases were

quarantinable in Boston: yellow fever, typhus fever, smallpox, and cholera. Since then have been added plague, diphtheria, scarlet fever, typhoid fever and measles, the period of time varying, of course, with the disease. New York quarantines yellow fever, measles, cholera, typhus or ship fever, smallpox, scarlatina, diphtheria, relapsing fever, and any disease of a contagious, infectious, or pestilential character, which shall be considered by the Health Officer dangerous to the public health. In Baltimore the quarantinable diseases are typhus fever, yellow fever, cholera, plague and smallpox. Other diseases may be added to this list at the discretion of the Health Officer. The uniform regulations of the Public Health Service call for quarantine in cholera, yellow fever, smallpox, typhus fever, leprosy and plague.

SCIENTIFIC BASIS OF QUARANTINE REGULATIONS.

It is evident from this brief history of the development of quarantine that the earlier regulations were entirely empirical and had little or no scientific basis. Indeed no matter how strictly they were enforced, the quarantinable diseases frequently got through quarantine despite every effort. Even the sanitary or military cordon was not entirely effective since cholera broke out in the city of Berlin in 1830 despite the protection afforded Prussia by her troops stationed along the Russian frontier. The failure of the old quarantine was the direct result of the lack of complete knowledge of the etiology and epidemiology of the very diseases against which protection was demanded. Quarantine became a pure science only when the science of parasitology was developed to a point where sanitary officials could know what to do, what measures to insist upon. With the advent of modern bacteriology beginning with the year 1878 quarantine regulations began to be applied with some knowledge as to the particular links in the chain of transmission of the various diseases which should be broken. A number of investigations had great influence in this regard. Chief among them must be placed the discovery of the cholera vibrio by Koch in 1883-84 and the development of a technique for its isolation from the stools and its proper identification. This gave an accurate method of making a diagnosis in all cases of suspected cholera, and Koch's cholera classes, which he personally instructed at the Gesundheitsamt in Berlin, revolutionized the methods of quarantine at first in Germany and soon over the civilized world.

As a result of the new knowledge brought by bacteriology the unexpected outbreak of plague in Bombay and Hongkong in 1893 and 1894 found a body of trained investigators ready to study the problem of the etiology and the epidemiology of the Black Death with modern methods. The work of Yersin and of Kitasato established the microbic origin of plague, and the subsequent investigations of a host of bacteriologists and sanitarians perfected our knowledge of its method of transmission. It may now be regarded as proven that the preventive measures which must be directed against plague depend entirely upon the variety of the infection. With the

pneumonic form it is the individual himself who is dangerous, the infection spreading from person to person through the agency of the plague-laden sputum. In bubonic plague entirely different conditions are met with. The individual himself is not dangerous. It is the infected rodent population from which the disease passes to man chiefly through the medium of insects (the rat flea for instance) against which quarantine measures must be directed. Bacteriology, however, has solved the problem of but two of the five great quarantinable diseases of the world. For two of the other three at least protozoology has furnished the clue. The investigations in this science which have led to the discovery of the important facts really began with the demonstration by Sir Patrick Manson that the disease filariasis produced by the nematode worm *Filaria sanguinis hominis* is transmitted to man by the bite of the mosquito which harbors the parasite. This discovery was followed by the work of Theobald Smith on Texas fever of cattle who showed for the first time in the world's history that a protozoan disease was transmitted by an insect host, in this case the cattle tick. As a result of these investigations it became possible for Walter Read and his band of devoted followers to prove that yellow fever, the scourge of the New World as plague had been of the Old, is carried only by the female form of *Stegomyia fasciata*. The clothing, the dejecta and the personal effects of yellow fever patients are entirely without infectivity. It is now an old story how the application of the work of Read, Carrol, Agramonte and Lazear enabled Wood and Gorgas to drive yellow fever out of Cuba, and Gorgas to keep the Panama Canal Zone free from this disease. Without this knowledge the Panama Canal could not have been built and the United States was just as surely doomed to failure as was the Republic of France. Furthermore this knowledge of the epidemiology of yellow fever has enabled the southern ports of the United States to keep this infection out of America and, in the few instances in which it has found entrance, notably in New Orleans, and in Brunswick, Georgia, to eradicate it without great loss

of life. Finally it has now been shown by the work of Nicolle in Algiers and by the investigation of Rickets, Anderson and Goldberger in Mexico City that typhus fever is also insect-borne, the hosts of the unknown parasite in this case being the body louse (*Pediculus vestimenti*) and the head louse, (*Pediculus capitis*). With smallpox we are still in the dark as regards the ultimate cause but have in the Jennerian vaccination an efficacious method of protecting the population and wiping out the scourge. Many problems must yet be solved, however, before quarantine can be perfect. The greatest needs relate to diagnosis. There is now no method to establish beyond dispute a diagnosis in a suspected case of yellow fever. This must still be done chiefly by elimination. Anderson and Goldberger, however, have given the world the method of diagnosing typhus fever by the inoculation of guinea pigs, a characteristic reaction occurring with all cases of this disease. The problem of bacillus carriers is also an urgent one especially in the case of cholera. In this infection Dunbar of Hamburg has shown that apparently normal individuals may harbor and excrete the bacillus and are capable of causing widespread epidemics, a discovery which Koch hailed as next to the discovery of the vibrio itself, the most important to be made in the epidemiology of Asiatic cholera. Whatever else may be needed in a quarantine station the services of a competent bacteriologist, with special training along certain lines and an up-to-date bacteriological laboratory with special equipment for making diagnoses of plague, cholera, and typhus fever, must be regarded as essential, as well as the presence in quarantine of expert physicians who can recognize with some certainty smallpox and yellow fever.

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NEW PUBLICATIONS.

The following six monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. HEWITT, M. D. 82 pages. Price, \$1.00.

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are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

TATTOO MARKS FOR THE IDENTIFICATION OF ANIMALS IN LABORATORIES.

By J. A. HUNNICUTT, M. D., and A. P. JONES, M. D.

(From the Hunterian Laboratory of Experimental Surgery, The Johns Hopkins University.)

Various methods have been employed for the identification of animals in laboratories.



TATTOOED INNER SURFACE OF RABBIT'S EAR.

For the larger animals, tags and detailed descriptions have

been relied upon, and for the identification of rabbits, cats and guineapigs, the cages have been marked and the animals carefully described. Sometimes stains have been used.

It occurred to one of us that tattooing might be simpler and more reliable than any of the means hitherto employed.

The inner side of the animal's ear has seemed, after repeated trials of other places, to be the best spot for the tattoo mark, which is made while the animal is under the influence of the anæsthetic.

India ink, a No. 9 seamstress' needle, and an artery clamp are the only articles required for the performance of the little operation. The inner side of the animal's ear is cleaned with 95 per cent alcohol and dried with gauze before tattooing. The needle is shortened by breaking off the tip, and the eye-end is sharpened to a point. The clamp serves as needle holder, and the eye of the needle as carrier for the India ink into which it is dipped. Letters or figures are made by a series of pricks with the sharpened eye-end of the needle, which is inserted into the skin at an angle of, perhaps, 25°.

We have been testing this method of indelibly marking our animals for several months and are well pleased with it.

IN MEMORIAM.

REGINALD HEBER FITZ.*

By W. S. THAYER, M. D.,

Professor of Clinical Medicine, The Johns Hopkins University.

It is a sad but grateful opportunity, that of coming home today to pay an affectionate tribute to the memory of my dear and valued master.

It is not far from thirty years ago, though it seems but yesterday, that we sat in the preeipitous amphitheatre of the then new school building in Boylston Street, and listened to his brilliant talks. No one who heard those remarkable lectures could have failed to carry away a deep impression of the strength, the ability, the learning of the man. They were remarkable lectures, remarkable in form and in substance; models of clear and precise exposition, admirably delivered in language, every faetted word of which seemed to have been so chosen that it, and it alone, could fill its place. Stimulating hours which gave to many of us a lasting realization of the importance of precision and accuracy in observation and thought and expression.

Fitz was not an investigator in the sense that he carried

out or led original, experimental research, but his contributions to the science and art of medicine were none the less important and valuable. His habits of discriminating precision in thought, in observation, in interpretation, in exposition gave him that penetrating clearness of vision which enabled him to extract, as could no one else, from a mass of apparently unrelated observations, the concise, clear, elinical picture, correlated with definite physiologieal and pathological processes and anatomical changes. It is no small achievement that this one man should have given to the world the first clearly defined description of two such important maladies as appendicitis and acute pancreatitis.

His communication entitled "Perforating Inflammation of the Vermiform Appendix, with Special Reference to its Early Diagnosis and Treatment," was delivered in Washington before the first meeting of the Association of American Physicians on the 18th of June, 1886, now more than twenty-seven years ago. In this study, the orderly system and simplicity of which are so characteristic of the man, he focussed clearly,

* Read at a Memorial Meeting at the Harvard Medical School, Boston, Mass., November 17, 1913.

for the first time, the vision of the medical world on the true nature of the inflammatory processes occurring so commonly in the right lower abdominal quadrant, and showed, convincingly, that the seat of primary disturbance, in the great majority of instances of this nature, lies in the appendix vermiformis. And along with this demonstration, he set forth in a masterly manner the clinical manifestations of the disease.

This publication came at a time when the world was well prepared. Everyone recognized that Fitz had, as it were, put his finger on the spot. Once set forth, the pathological and clinical sequence of events seemed almost obvious—obvious as are so many great truths when once they have been clearly enunciated. The sharp light thrown by Fitz on this common and perilous pathological event brought it about that our countrymen were fully ten years in advance of the rest of the world in their comprehension of this process, and in their skill and efficiency in the care of the patient.

How many human beings owe their lives to-day, more or less directly to Fitz, no one can tell. Surely, it is no small number.

There has been one curiously paradoxical sequence of this great contribution. The word "appendicitis" employed by Fitz in the course of this article was immediately seized upon by the public and has entered into universal use, but not without bitter protest from some who still shudder at its etymological hybridism.

It is an amusing thought that of all men, Fitz, the most careful and accurate, should have been the target of irritated critics, because of the introduction into medicine of what they regard as an ill-constructed word.

The practical importance of the facts set forth in this first contribution has, it has often seemed to me, somewhat overshadowed the brilliancy of the later work. In his studies on the appendix, the truth seemed so nearly ready to emerge of itself that the medical public grasped, immediately, the significance of the exposition. The lectures on acute pancreatitis, on the other hand, treated of a subject of which little was generally known, even anatomically. The analysis of the carefully collected pathological material, the discriminating consideration of the clinical features and the final synthesis of the definite, convincing clinical picture of the disease, acute pancreatitis, was truly a great achievement.

How well I remember the demonstration by Virchow, nearly a year after the delivery of the Middleton Goldsmith lectures, after I had seen acute pancreatitis recognized clinically and confirmed at necropsy—how well I remember the demonstration by Virchow of the organs from a case of disseminated fat necrosis with sequestration of the pancreas, accompanied by the observation that these instances were pathological curiosities. With what pride I sought him out and made him familiar with the little pamphlet which set forth so clearly and so simply the clinical aspects of the disease!

How vivid is the memory of Fitz's recitations and demonstrations! What student who attended them can forget the charm of that subtle and incisive, but yet humorous and not unkindly irony—or rather, perhaps, that ironical face-

tiousness which so disconcerted some of his pupils and colleagues, and so delighted others; which was, I am sure, highly beneficial to many who did not fancy it at the moment.

One did not go to sleep in Fitz's demonstrations!

By nature of a careful and judicious temperament, he was a strong man, and had the strong man's love for discussion, argument, opposition. Just and tenacious of his opinions as a strong man should be, his firm mind was not easily shaken. But firm though his mind was, it was ever open to recognize and welcome and embrace the new truth. This very attitude of apparent opposition was one of Fitz's most stimulating qualities, inciting his associate, whether student or colleague, to keener and more efficient effort.

At the necropsy table he sought to induce the clinician to express a definite opinion as to the nature of the case, and, where there proved to have been any failure wholly to apprehend the character or extent of the pathological process, he often pointed out the omission in diagnostic procedure or the error in reasoning which had been responsible for the incompleteness of the diagnosis. This most instructive and valuable habit was trying to some over-sensitive colleagues. But Fitz was consistent; he did not spare himself. While yet pathologist at the Massachusetts General Hospital, he used to visit, in the surgical wards, patients on whom an abdominal section was to be performed, in order that he might compare his bedside observations with the results of surgical investigation. His opinions he was always willing to express, far more willing, sometimes, than those in attendance upon the patient. This habit must have been of great assistance to him as a consultant in later years; as an example to the house officers it was invaluable.

Fitz's peculiar keenness of intellect inspired, at first, in certain of his students, an admiration and respect not untinctured with fear—something akin to the *Ehrfurcht* of our Teutonic brethren. But the element of fear dissolved into love with the first personal contact. How simple and gracious was his reception of the student who, perhaps, with some misgiving, sought his counsel in private! His unfailing kindness and thoughtfulness, his friendly interest and wise advice so freely and generously given, meant more to some of us than words can express.

To not a few of his students, his teaching and example were the great inspiration of their school days, and to most of these men this inspiration has been a lasting and a growing influence. There must be many who owe to him their best ideals in medicine, and surely, there are others of his pupils who have been, as have I, so jealous of his regard that any consciousness of lapse or shortcoming has been inevitably associated with the sting of the thought that they were unworthy the confidence of Fitz.

It is very strange and sad, the thought that all this wealth of wisdom and learning and experience so slowly and painfully acquired through a long and active life, has vanished in a moment. It leaves one with a sense of immense emptiness and vacuity and waste.

But he has left to mankind a large legacy in his epoch-making contributions, and with his students and disciples he remains ever present, embodied in their highest ideals. If these disciples shall succeed in shaping their lives as he might have wished, his beneficent influence will long endure.

TWO MEN:

GEORGE ALEXANDER GIBSON
HUGH ANGUS STEWART.*

By W. S. THAYER, M. D.,

Professor of Clinical Medicine, The Johns Hopkins University.

Seven years ago, there came to us from Edinburgh, a young man who desired to spend a year at work such as might enable him to prepare the thesis necessary for the acquisition of his doctorate in medicine. This young Scot brought with him letters from his former master in Edinburgh, a man distinguished in his profession and very dear to his friends. The affection that the pupil always showed toward his master and the almost loving interest with which the master inquired for his pupil on those too rare occasions when it was my good fortune to be thrown with him, have brought it about that these two men, in some ways very different, have been closely associated in my mind.

By a strange fate, both of these men, seemingly so full of life and strength and vigor, have gone within a few months of one another.

The world was ill able to spare them.

I cannot refrain from saying, at the outset, a few words of the master from whom Hugh Stewart drew much of his inspiration, the man who gave him that advice which brought him to us.

George Alexander Gibson was born in Perthshire, in 1854, and graduated in medicine in Edinburgh in 1876, taking his degree of M. D. in 1881. In 1874 he had already obtained the degree of B. Sc. at the same university. A fine, spirited, able fellow, he soon attained eminence as a practitioner and a teacher, and his visits and clinics at the Royal Infirmary were greatly appreciated by a wide circle of students. He was a member of many learned societies and his contributions to medical literature were numerous and valuable. Gibson was an able clinician and a successful teacher, but above all he was a man of unusual personal magnetism. He was not a great investigator; he had conducted no notable, original experimental work, but he was an excellent observer, a clear, forceful teacher, and he had a remarkable power over his fellow men, a power always for good; sane, wholesome, stimulating. Of a large frame, with a ruddy complexion, Gibson's clean-cut features might have sprung from some eighteenth century portrait, and the fresh glow of his countenance seemed

to permeate the air about him with a spirit of confidence and optimism, an indescribable sense of the joy of life; for Gibson had a rare and mellow human charm. The joy of life was ever in him—on the golf course; rod in hand by the rushing stream; in his library, reading with sympathy the works or the life of some master of his art, rejoicing in the wit and wisdom of a Holmes, with every incident in whose life he was familiar, chuckling over some crystalline epigram of an Anatole France whom he loved to quote; in his wards, surrounded by his students, or about his more than hospitable board—the joy of life was in him and radiated warmth and health and happiness upon those who surrounded him. Wherever he was, his ear was always ready, his eye was ever open to seize some unexpectedly humorous aspect of the situation. He was kindness itself. He loved his fellow man, and his fellows loved him. There are many of us here in America who remember him with warm admiration and affection.

Such a man, if he has, as had Gibson, sound training and natural clinical ability, cannot fail to be an inspiration to his pupils. His great work lies, not so much in his own original contributions to medical science as in the influence which he has upon those about him—pupils, friends, patients. Freed by his nature from the blinders of vanity and pride, such a man knows and weighs his own limitations as well as those of others, and is often the best and wisest adviser to the youth who desires to enter upon a more strictly scientific career. Such a man George Gibson seemed to me, and as such a man Hugh Stewart loved him and looked up to him.

At even so recent a period as seven years ago it was by no means customary for a European student to seek, in an American laboratory or clinic, the opportunity to pursue post-graduate study. But Gibson realized the importance and the value of a cosmopolitan education and experience, and so it was that we came to know Hugh Stewart.

Stewart also was a Highlander, accustomed as a boy to the Gaelic tongue—a Scot by birth, by nature, by tradition, by education. From a youth passed amid the wild beauty of those purple moors and hillsides which for centuries have nourished some of the sturdiest of our British stock, he drew all the vigor and strength so characteristic of that wonderful people—that strain which, springing from a remote corner of a little island, is so inseparably bound to all that we most love and treasure in history, in romance, in poetry, in art, in science, in literature, in statecraft—which has contributed so largely to all that makes for the greatness and stability of our race. Tall but so well proportioned that he never impressed one as a strikingly large man, with fine, expressive features, Stewart had a quiet, modest, rather diffident manner. He was a man of few words, and he never spoke about himself. Of his early life, even his best friends knew little, for he rarely dwelt upon it.

At the outbreak of trouble in South Africa, Stewart entered the army as a volunteer, and served creditably. He referred, occasionally, with some humor, to the circumstance that, for a time, his duties put him in charge of a number of army

* Remarks made on the occasion of the dedication of a memorial tablet to Hugh Angus Stewart, M. D., Columbia University, N. Y., November 15, 1913.

mules which had been imported from the United States. I regret to say that his opinion of the moral character of those mules was such as to inspire a distrust which I was never able wholly to shake, as to the business probity of those of our countrymen who had been instrumental in furnishing these important engines of war.

Quiet and modest as was his demeanor, he was one of the strongest and most self-sufficient characters I have ever known. His problem once chosen, he went to work with an all-absorbing energy and persistency. Remarkably resourceful, he rarely asked assistance or advice. He framed his own plans, devised his own instruments and pursued his problem to its end in an orderly and systematic manner. During his first year in Baltimore, he carried out, in Dr. Hirschfelder's laboratory, the excellent piece of work on the pulse and blood pressure changes in aortic insufficiency, which earned him his degree of M. D. and a gold medal.

After returning to Edinburgh to receive his well-earned honors he came again to Baltimore in the fall as my assistant. His duties in this capacity were numerous and not always easy, but he found time, nevertheless, to carry out some exceedingly interesting and ingenious experiments which apparently demonstrated that the circular muscle fibres below the aortic and pulmonary valves enter into contraction slightly later and remain in contraction somewhat longer than the rest of the ventricular muscle. In the course of this work, he showed remarkable mechanical ingenuity in devising a delicate instrument for the graphic registration of these muscular contractions. Why these experiments were not recorded I have never known. Stewart was not one who rushed into print and it is probable that he felt that there was still something lacking to make the demonstration complete and his results unassailable.

He was an admirable assistant, ready, understanding, far-seeing, and he soon showed himself to be a man of excellent clinical judgment. His most valuable qualities were, I should say, his self-sufficiency and his independence. Deferential, never obtruding his opinion, he always knew his own mind, and if the opportunity offered, he expressed his views, whether or not they agreed with those of his superior officer. He was fond of argument, showing, in rather high degree, an inclination to take up opposition to any sharply enounced proposition, a tendency which was so striking in an honored leader of the medical profession in America, whose untimely death we have so recently had to mourn—my dear old master and friend, Dr. Fitz. But there is no more valuable habit of mind than this when it is associated with a fundamentally open and judicial temperament; it is an attitude which, as I have often said of Fitz, is characteristic of the strong man—and Stewart was a strong man.

I can see him now: We were perhaps discussing some question of interest, and, in my enthusiasm, I had expressed my views at some length and rather positively. Stewart had listened with perfect deference but when I was done, he would lower his head a little, as if he were about to charge some obstacle, and in a quiet, determined manner, with a slight Scotch accent, he would say, "I don't think so"—and he

was generally able to give good reasons why he did not think so.

After a year's service as Assistant Resident Physician, Stewart became Assistant in Pathological Physiology in the Johns Hopkins University, and a Fellow of the Rockefeller Institute. During this year, he carried out with Dr. King some important experiments in which it was shown that the toxic element of the bile, that which causes the lowering of the blood pressure and the slowing of the heart, lies in the pigments and not, as is still so commonly asserted, in the salts. Following this, Stewart published an interesting note on "The Dextrose Consumption by the Isolated Perfused Human Heart."

In 1909, he left Baltimore to become the Associate of Dr. MacCallum, as Assistant Professor of Pathological Anatomy in Columbia, and it was with most sincere regret that we parted with him. That which he accomplished in these last four years, I need not tell you.

Stewart had always desired eventually to enter into clinical medicine, and alongside of his experimental study in the laboratory and his teaching, he kept in touch with the patient at the bedside in St. Luke's Hospital. In medicine his especial interest was in the study of the circulatory system, an interest stimulated, undoubtedly, by his work with Gibson. The list of his valuable contributions shows how consistently he pursued the course that he had chosen at the outset.

To all he seemed a man of exceptional promise, one who must surely have made his mark.

The master, essentially a clinical observer, had impressed upon the pupil the desirability, in the new day, of preparing himself for a career in medicine by years of fundamental study and research, that he might be fitted properly to direct the many activities of a modern medical clinic. And there were few men in America better fitted for such a career than was Stewart at the time of his death. Reserved, undemonstrative, retiring as he was, it was not difficult to see that Stewart was a man of really deep feeling and of rare loyalty. For Stewart was a man—a man in the purest and best English sense of the word—a man on whom one felt instinctively that he could rely in any emergency. And after all, is it not this which means most to us in this world? What skill, what brilliancy, what powers, what accomplishments move use as do those qualities of sturdy and efficient self-reliance and courage, and honesty and directness which go to make a man! What triumph of genius stirs us as deeply as does the simple story of a Scott and an Oates!

And with all his ability and his talents, it is this indefinable essence of manliness that appeals to us most profoundly, as we think of the fine fellow in whose memory we meet today. There are few of us who knew him who, in our hearts, have not more than once said, "Would that I were a little more like Stewart!"

LIST OF PUBLICATIONS OF HUGH ANGUS STEWART.

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Stewart (H. A.): Experimental and Clinical Investigation of the Pulse in Aortic Insufficiency. Arch. Int. Med., Chicago, 1908, I, 102-147.

King (J. H.) and Stewart (H. A.): Effect of the Injection of Bile on the Circulation. J. Exper. M., Lancaster, Pa., and N. Y., 1909, XI, 673-685; also Tran. Assn. Am. Phys., Phila., 1909, XXIV, 396-409.

Stewart (H. A.): The Dextrose Consumption by the Isolated Perfused Human Heart. J. Exper. M., Lancaster, Pa., 1910, XII, 59-66.

Stewart (H. A.): The Cause of Cardiac Cohypertrophy. Proc. Soc. Exper. Biol. and Med., N. Y., 1910-11, VIII, 13.

Stewart (H. A.): An Experimental Contribution to the Study of Cardiac Hypertrophy. J. Exper. M., Lancaster, Pa., 1911, XIII, 187-209, 4 pl.

Stewart (H. A.): The Influence of Salts of Calcium and Potassium on the Degree of Hypertrophy Produced by Adrenalin Infection in Rabbits. Proc. Soc. Exper. Biol. and Med., N. Y., 1911-12, IX, 7.

Stewart (H. A.) and Harvey (S. C.): Variations in the Response of Different Arteries to Blood Serum and Plasma. Proc. Soc. Exper. Biol. and Med., N. Y., 1911-12, IX, 84-87.

Stewart (H. A.) and Harvey (S. C.): The Vaso Dilator and Vaso Contractor Properties of Blood Serum and Plasma. J. Exper. M., Lancaster, Pa., 1912, XVI, 103-125.

Stewart (H. A.): The Mode of Action of Adrenalin in the Production of Cardiac Hypertrophy. J. Path. and Bacteriol., Cambridge, 1912-13, XVII, 64-81. 2 pl.

Stewart (H. A.): On certain Relations between Lipoid Substances and the Adrenals. To appear in the transactions of the XVII International Medical Congress.

DR. JULIUS PREUSS.*

By DR. DAVID I. MACHT.

I am happy to have the privilege of addressing a few words to this society about one who is probably unknown to most of you, and yet one with whose work every student of the history of medicine should be familiar. I am referring in particular to the students of medical history in the broader sense of the word. Those who are interested in that subject may be divided into two groups. We have, on the one hand, men who are fond of cherishing the memories and singing the praises of some excellent old local worthy, or of some honored and admired leader in the line in which they are particularly engaged. On the other hand, we find the broader, the cosmopolitan, or as we may style them, philosophical type of students of the history of medicine, who regard that subject not from the local or even national point of view, but as a phase and an important one, of the history of civilization.

To such a student, the history of medical science among the other nations and races is of especial interest. But unfortunately the access to the literatures of other nations than those of Western Europe is a difficult one, and so our acquaintance with the medicine of the Orient, for instance, is but a very superficial one. This is particularly true of Ancient Hebrew and Arabic medicine. Although a number of monographs in this field have from time to time appeared, the information

which they contain was gathered either indirectly at second hand, or by some one unfamiliar with medicine.

Thus, for instance, of the two most important works on Biblical and Talmudical medicine until recently, one published in 1860 by Wunderbar was by a *layman*, and the other appearing in 1901-1903 by Prof. Ebstein, was by a great physician but one unfamiliar with the Semitic language and literature. What that means can hardly be appreciated by one who knows nothing of the Hebrew or Arabic tongues—their briefness, conciseness, and force. They describe but little, but the rich significance of their verbal roots paints in one word the picture of a complicated subject. It was not until the publication of the "Biblisch Talmudische Medizin" of Julius Preuss, in 1911, that we really acquired a reliable, comprehensive, and scientific exposition of the subject, by a first-class physician on the one hand, and a thorough Semitic philologist, who made the history of medicine his life's study, on the other. It is of this author, who but recently passed away, and of his work that I wish to say here a few words.

Julius Preuss was born in a small village, Gross-Schönbeck, in the Mark of Brandenburg, Prussia, in 1861. After going through the public schools in the town of Angemünde, he entered the gymnasium at Prenzlau, where he distinguished himself by his brilliant scholarship. Upon graduation he went to study medicine in Berlin, and there upon the completion of the course the newspapers contained an interesting account of the brilliant young doctor, who achieved the rare feat of having passed Virchow's examination with the highest marks. Virchow stated that he knew *medizinisch zu denken*, how to think medically. He went back to his native town to practice, but soon returned to Berlin in order to be in close contact with the great minds in that center of learning. Here he practised for a living, and studied and wrote; and here he passed away after a protracted illness on September 23 last.

Preuss was the author of numerous medical papers, which, however, do not interest us here. His chief contributions to medicine were his historical papers, which culminated in the great work on "Biblisch Talmudische Medizin," completed shortly before his death.

This book, as may be seen at a glance, is a standard work, and promises to remain the authoritative reference book on the subject for a long time to come. A survey of its contents will show that the author made it his life study. Preuss can be well styled as the Boswell of Ancient Hebrew Medicine. His work is a classic which is to be classed with only a few great ones on the history of medicine, such as, for instance, that of Haeser.

Being a strictly orthodox Hebrew, he from his earliest youth devoted time to regular readings in the Talmud, Midrashim, and other Ancient Hebrew and Aramaic texts, and as an ardent student of medicine he jotted down and kept notes of every medical reference that he would come across as may be seen from the numerous references in the text. These he compared and classified, and finally compiled in the work before us.

* Read before the Johns Hopkins Hospital Historical Society, Dec. 8, 1913.

I should earnestly recommend every one desiring to trace the history of some medical subject back into antiquity to consult this book. There are but few subjects in medicine upon which it does not touch. Here is a brief résumé of its contents:

The first chapter treats of the physician in *general*, his position, education and training.

The second chapter contains extremely interesting data on anatomy and physiology, covering over one hundred pages.

The third chapter treats of general pathology and therapy.

The fourth chapter deals with special pathology and therapy.

The fifth chapter is on surgery. Here we have a description of various kinds of wounds, different operations, sleeping medicines, etc.

The sixth chapter deals with diseases of the eye.

The seventh chapter contains some extremely interesting information about ancient dentistry.

The eighth chapter is on diseases of the ear.

The ninth chapter is on diseases of the nose.

The tenth chapter describes a number of nervous affections, epilepsy, hysteria, headaches, palsies, sciatica, etc.

The eleventh chapter is devoted to a consideration of some psychiatric conditions.

The twelfth chapter treats of skin diseases.

The thirteenth and fourteenth chapters deal with gynecology and obstetrics.

The fifteenth chapter is a discussion of materia medica and pharmacology.

The sixteenth chapter is a very important and interesting one on legal and social medicine.

The seventeenth chapter is a treatise on hygiene.

The eighteenth chapter is on dietetics.

Last but not least important of all, the book contains a complete bibliography.

I do not intend to take more of your time, by going into a detailed description, but if these few remarks may serve to impress upon your memories the title of this book, I am sure I have not spoken in vain, and I know that it will be a most acceptable tribute to the memory of my friend, its author.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

November 3, 1913.

Interpretation of the Auscultatory Blood Pressure Sounds. DR. D. R. HOOKER AND MR. J. D. SOUTHWORTH.

The accuracy of Korotkoff's method for the determination of diastolic arterial blood pressure in man has been questioned on the ground of clinical and experimental observations. The authors obtained a graphic registration of the vascular sounds by the use of a telephone and capillary electrometer (method of Einthoven and Geluk) and compared them with a synchronous graphic record of the excursions of the lever of an Erlanger sphygmomanometer. In sixteen records from four normal individuals there was perfect agreement between the two records for the points of systolic and diastolic pressures. Several of these records were exhibited. Tests of the delicacy of the method of sound registration convinced the authors of its reliability; and they therefore concluded that, at least in the cases observed, the auscultatory method is reliable for the determination of the diastolic as well as of the systolic arterial blood pressure in man.

DISCUSSION.

DR. BARKER: Since the appearance of Korotkoff's publications we have been using the auscultatory method of deter-

mining blood pressure in the clinic here, especially for the diastolic pressure. Dr. Hirschfelder and I were very interested in the method and found it clinically accurate. At our request Drs. Engle and Allen controlled the method with the Erlanger instrument. They found the maximal pressure to be entirely accurate when determined by the auscultatory method; the minimal pressure agreed within 5 mm. of mercury. The method is not applicable in cases of aortic insufficiency on account of the sound audible over the artery even when no pressure is applied in the cuff.

There has been some dispute as to the exact moment which corresponds to the minimal pressure. As the minimal pressure is approached on the way down from the maximal pressure one hears first certain murmurs over the artery, then a sudden accentuation of the sound, a little lower an enfeeblement of the sound, and then a disappearance of the sound altogether. The last three phases do not cover a variation of more than a few millimeters of pressure so that for clinical purposes it is really unimportant which point of the three is chosen to represent the minimal pressure. It would be interesting, however, for scientific purposes to determine by Dr. Hooker's method which one of these three points corresponds precisely to the minimal pressure.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice; abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXV is now in progress. The subscription price is \$2.00 per year.

(Foreign postage, 50 cents.) Price of cloth-bound volumes, \$2.50 each.

A complete index to Vol. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

NOTES ON NEW BOOKS.

Manual of Human Embryology. Edited by FRANZ KEIBEL AND FRANKLYN S. MALL. In two volumes. Volume II, with 658 illustrations. \$10.00 (*Philadelphia and London: J. B. Lippincott Company, 1912.*)

The editors explain in the preface that the delay of more than one-half of a year beyond the expected time of publication of this volume is partly due to the fact that the sections on the heart, blood vessels and sense organs were completed by others than those who originally undertook the work of writing them. In justice to some of the authors in the matter of literature references, it should be stated that their articles were finished more than a year before the publication of the book.

Dr. Streeter discusses the development of the nervous system under four subdivisions: (1) Histogenesis of nervous tissue; (2) Central nervous system, (3) Peripheral nervous system, (4) Sympathetic system.

In the description of the structure of the neuroglia and partly in the histogenesis he follows the work of Hardesty. In the discussion of the various theories of the histogenesis of nerve tissue, proper credit is given to Harrison's work, which Streeter accepts as proving that the outgrowth theory of His is correct. He also derives the sheath cells from the ganglionic crest and advocates the theory that the T-shaped processes of ganglion cells are due to branching rather than to approximation by unequal growth of the perikaryon. Contrary to former opinion, he considers that a neurolemma is present on the nerve fibers of the central nervous system.

In referring to the optic evagination as constituting the "eyeball," he makes an erroneous use of the term. We notice the omission of the epithalamus in the list of the derivatives of the diencephalon and the inconsistent use of the terms ventral, dorsal, anterior and posterior, diencephalon and thalamencephalon.

Streeter favors the views that the rhombic grooves are branchiomic rather than neuromeric, as hitherto considered.

On page 40 the *lamina terminalis* is spoken of as forming the anlage of the rhinencephalon and on page 47 line 7 he says "a depression for the organ of smell appears lateral to the *lamina terminalis*," and on page 90 again, "in embryos under four weeks old the rhinencephalon can only be recognized as the space between the *lamina terminalis* and the internal ridge formed by the corpus striatum."

He is in agreement with Patterson that the dorso-median septum of the spinal cord is, to some extent at least, formed by the obliteration of part of the neural canal.

The description of the development of the pituitary and pineal bodies is not very satisfactory and the term "vascular epithelial sprouts" is certainly open to objection.

In the development of the interforebrain commissures, Streeter follows the descriptions of Smith and Marchand. His suggestion that the term fissure in contradistinction to sulcus be reserved for the Sylvian and longitudinal will probably not be adopted. There is no consideration of the development of the individual fissures.

The description of the development of the nerves of the extremities is based chiefly on the work of Lewis and Bardeen, and in the case of the cranial nerves Gaskell's functional system is followed so far as possible. The sympathetic system is considered as ectodermal in origin without any reservation.

A few minor errors are noticed, as the omission of the article on page 56, line 4, and the incorrectly stated legend under figure 99.

The subject on the whole, is treated with considerable breadth of vision and is quite satisfactory. Many of the numerous illustrations are original.

Zuckermandl, who is especially well fitted by his own researches, contributes a short but excellent chapter on the development of the

chromaffin organs. He considers that the suprarenal cortex is derived from the mesothelium and the medulla from the sympathochromaffin tissue, and calls attention to the fact, of practical importance that accessory suprarenals may be found embedded in cavitics in the suprarenal and may be mistaken for adenomata.

Franz Keibel contributes the chapter on the development of the organs of sense. He holds the view that the muscle spindles are not sensory; accepts Peter's idea that an unpaired olfactory plate occurs in all vertebrates; takes issue with His as to the identity of the *processus globularis* and that the nasal septum had a paired origin, and objects to Peter's verdict that Jacobson's organ is often destroyed in the adult by frequently repeated catarrh. Attention is called to the practical fact that the septal folds may persist and by hypertrophy form tumor-like structures. At the end of the section on the nose follows a brief and inadequate account of malformations in the nasal region. The illustrations are drawn largely from Peter and Killian.

In the section on the development of the eye, Keibel maintains that all attempts in the past to derive the vertebrate eye from the invertebrate have been unsuccessful. He calls attention to the fact that all cases of coloboma cannot be explained by the failure of the closure of the chorioidal fissure; follows Grynfeldt and Nussbaum in developing the muscles of the iris from the ectodermal outer layer of the optic cup, and the description of Fleischer and Matys as to the development of the lachrymal passages. Attention is called to the lack of a satisfactory account in man of the development of the ocular muscles and to the desirability of a much more complete study of the post-fetal growth of the eyeball as perhaps throwing light on the development of myopia.

The results of Streeter and W. His, Jr., have largely been followed in the development of the internal ear, Hammar in the case of the middle ear, and His' and Schwalbe's account of the development of the auricle. Properly enough, Keibel criticises the too great credulity of the anthropologists as to the significance of the ear forms in criminals. However, a more extended consideration of the embryology of anomalies of ear forms would be desirable.

In the chapter on the development of the alimentary canal F. T. Lewis contributes the sections dealing with the intestines, œsophagus, stomach, liver and pancreas; McMurrich the sections on the mouth and its organs, and Grosser the section on the pharynx and organs of respiration.

Lewis' presentation of the subject is very acceptable, although in some cases he goes into very great detail. Many of the illustrations showing the development of the stomach and intestines are taken from Johnson's work. He accepts as proven the early atresia of the duodenum, but not of the œsophagus, and denies that duodenal glands are extensions of the pyloric glands. A more extended description of the histogenesis of the villi would be a desirable addition.

In the development of the liver he thinks that it is not merely an invasion of the lumen of the vein but that there is a mutual process which he calls an intercrecence. This difficult subject is well handled, due credit being given to the work of Mall and others. He finds that double ventral buds of the pancreas as described by Helly and Kollman are unusual, and that the embryological development of the islands of Langerhans does not accord with the idea that they represent a phase of glandular activity. From the discussion it is evident that our knowledge of the development of these bodies is not in a very satisfactory condition. The account terminates with a brief consideration of pancreatic anomalies.

Grosser's contribution is a satisfactory presentation of a difficult subject. He calls attention to a remarkable ventral and irregularly knobbed process filled with mesoderm and projecting from the closing membranes into the pharyngeal lumen. He interprets this

as possibly a rudimentary internal gill. Stohr's view that the lymphocytes of the tonsil are derived from epithelium is favored, and that the carotid body is from the chromaffin system rather than branchiogenetic. He introduces the term ultimo-branchial body for the lateral part of the thyroid. The statement that the widely divergent opinions of various authors concerning the condition of the post-fetal thymus is due to accidental involutions during illness is not a satisfactory explanation to the writer. On page 467 the term cervical is used by mistake for cortical. The reader of this section is left with the impression that our knowledge of the subject is in an unsatisfactory condition.

Grosser considers the lung anlage symmetrical and in this disagrees with the work of Norath and Flint and believes that no final statement can at the present time be made as to whether the branching is monopodial or not. The illustrations are numerous and drawn from several sources.

The development of the blood and vascular system is treated by several authors. Minot contributing the part on the blood, Tandler dealing with the heart, Evans with the vascular system, and Sabin the lymphatic system.

Minot justly arraigns the present nomenclature of the blood cells and blames the clinicians largely for the unscientific terminology. He boldly discards the old terms and proposes an entirely new one, dividing the erythrocytes, a group term, into the ichthyoids, sauroids and blood plastids (non-nucleated form). He considers the primitive mesamæboids as the ancestors of all blood cells and therefore red and white corpuscles arise monophyletically. He states clearly what we know and do not know about blood development. The leucocytes are divided into

{	{	non-granular	
		{	fine granules
			coarse granules
			degenerating

Eosinophile granules he considers devoured fragments of red blood cells and not endogenous in origin. He holds the opinion that genuine blood platelets occur only in mammals and follows Wright's theory of the development of the platelets. On page 511, line 13, evidently *by* is intended for *but*. On the whole this section is the most original in the methods of presentation, most stimulating in ideas and one of the best in the book.

Tandler largely follows Mollier on the early development of the heart and Born on the later development. He describes in great detail the bends, twists, constrictions, etc., but does not always state the age of the embryo in relation to the development stages described. On page 42, line 2, the term fibrous is hardly a good histological term as used here. The histogenetic changes are not very thoroughly considered and a brief discussion of the anomalies of the heart would be a desirable addition. On page 543 the text reference should be fig. 377, instead of 397.

The section on the development of the vascular system contributed by Dr. Evans is, to a large extent, original and is a very excellent presentation of a difficult subject. The illustrations are numerous and for the most part very good. The introductory part is a general discussion of the origin of blood vessels, and the second part deals with the special development of the vascular system and chiefly with the main vascular trunks. He considers that it is impossible yet to give a decisive answer to the question of the origin of the blood vessels in the body, but his account indicates that already considerable is known and that recent additions are extensive, especially as indicating the method of transformation of the primitive blood vessels into the adult type.

He formulates the fundamental conception of the development of blood vessels essentially as follows: Blood vessels tend always to be laid down in multiple capillary anlage rather than single trunk-like forms, and the trunks are made by the preservation and enlargement of some vessels, while the others disappear and

hydrodynamic grounds determine what part of the plexus shall be preserved as vascular trunks. The strong growth of a region drawing the blood to it, and the tendency of the blood stream to take the shortest path, constitute some of these hydrodynamic factors.

The following errors were noted: On page 606 *T. a.* of the plate subscription is lacking in the legend of the illustration. On page 588 we notice the incorrect spelling *posses*; on page 641, *perisodactyle*; on page 643, *cerical*, and on page 690, *branchial* for brachial. On page 641, line 12, *upper* is a very poor substitute for dorsal.

The chapter on the development of the spleen and lymphatics by Dr. Sabin will be especially interesting to American anatomists who have followed the controversy as to the method of lymphatic development. She adheres steadfastly to the sprouting theory. We notice on page 740 the error in *synecytium*. This article is well illustrated and is a satisfactory presentation of the subject.

W. Felix, in a long section of some 230 pages, gives a very elaborate discussion of the development of the urinogenital organs. The illustrations are numerous and many are original. He considers that the first six pronephric segments show dysmetamerism and that the pronephros is better developed in man than any other mammal, lacking only the internal glomerulus.

On page 800 we find the statement that the pronephros extends from the fifth cervical to the third thoracic segment, and on page 819 that the pronephric tubules are never found caudal to the first thoracic segment. An elaborate table is given showing the length of the mesonephros expressed in segments and the number and position of the mesonephric tubules. Also attention is called to the important fact that a cystic kidney may be due to a failure of the terminal collecting tubules to find and fuse with the intermediate tubules. The post-fetal growth changes of the kidney are described and finally kidney malformations are discussed. The view is held that in man the bladder is ventro-cloacogenic rather than allantoidogenic, and that there is no internal descent of the testis or ovary. We note that no embryological explanation for *ectopia vesicae* is offered.

The volume closes with a discussion by Keibel of the interdependence of the various developmental processes, accompanied by a comparative table. A literature list follows each section throughout the book.

This volume is even less adapted than the first as a text-book for students, but as a reference book it is unquestionably a classic and should be in the hands of all anatomists and biologists. Mistakes are few and there is little for criticism and the reduplication which is a natural result of multiple authorship is not excessive. Anatomists everywhere will regret that Dr. Mall is not a contributor to this volume.

Oxford Medical Publications: Gout. By JAMES LINDSAY, M. D. \$1.50. (London: Henry Frowde and Hodder & Stroughton, 1913.)

American physicians and medical students, who have few opportunities to see cases of gout, will find this work in excellent résumé of the subject. In a brief but clear and comprehensive review of the subject the author brings out the essential points in his discussion of its aetiology, pathology, symptoms and treatment.

Headache. By DR. SIEGMUND AUERBACH. Translated by ERNEST PLAYFAIR, M. B. \$1.50. (London: Henry Frowde and Hodder & Stroughton, 1913.)

Symptoms are not as frequently or carefully considered by students as diseases, but a thorough study of a symptom may often elucidate fully the whole trouble. How many physicians or students, when a patient complains of headache, really stop to con-

sider what this symptom may indicate—how it arises, what nerves are affected, etc. Headache is only a certain form of pain, and pain no matter where situated is but a symptom, and practitioner must learn to look at it so, and remember that every symptom has its cause, and that he will not cure the cause by simply eliminating the pain with some form of analgesic. Because headache is so common we are all apt to consider it but a trifle except in these rarer instances where the pain is persistent or severe, and as a result our treatment of headaches is frequently worse than none at all, for we treat it without due thought. For students and physicians, who haven't a clear idea of the various forms and nature of headache, and how it should be treated, this well-written treatise of Auerbach will be most helpful. The following is his classification of headaches: A. The more independent forms (migraine, neurasthenic, rheumatic); B. Those associated with diseases of individual organs (brain, special senses, digestive tract, kidneys); C. Those in general diseases; and D. Contractions of different forms. The book is not too long for a busy doctor to read through with care, and yet the subject is so lucidly handled as to give the reader a very clear idea of not only its variety, but its importance.

The Modern Hospital. By JOHN ALLAN HORNSBY, M. D., and RICHARD E. SCHMIDT, Architect. Illustrated. (Philadelphia and London: W. B. Saunders Company, 1913.)

This volume of over 600 pages is an exhaustive work on the inspiration, architecture, equipment and operation of hospitals. The authors have treated the subject in detail and the chapters on "The Surgical Operating Room," "Business Management" and "Purchase of Supplies" are especially good.

In a work of this kind it is doubtful if the authors should enter into the description and detail of the administration of anæsthetics, of the uses of hydrotherapy and of minor surgical technic. Such subjects are more in the realm of therapeutics and surgery than of hospital administration. In many instances, too, there seems to be a lack of finality of discussion in certain subjects—leaving the reader in doubt as to the correct course to pursue. More space could well have been given to the subject of social service and outpatient work—branches of hospital administration which have, of late, assumed large proportions.

At the same time the book fills a longfelt want. The illustrations are very good, the text clear and the subject is presented in an interesting manner.

Medical and Surgical Reports of the Episcopal Hospital, Philadelphia. Vol. I. (Philadelphia: Press of Wm. J. Dorman, 1913.)

It is a pleasure to note the appearance of a volume of reports from this hospital. All large hospitals should issue such or similar volumes annually, for in this way much valuable hospital work secures a recognition, which it would otherwise fail to obtain. The larger number of reports in this volume are surgical, and a few of them have been already published elsewhere. Some of them are illustrated, and there are other illustrations descriptive of different parts of the hospital. The volume is in all respects worthy of this well-known and highly respected hospital.

A Manual of Otology. By GORHAM BACON, M. D., etc. Sixth Edition, Revised and Enlarged. Illustrated. \$2.25. (New York and Philadelphia: Lea & Febiger, 1913.)

The merits of this manual have long since been recognized by the profession, and the present edition, with new material, will continue its popularity. The author's method of presenting his subject is attractive, and makes the book especially suitable to the student and general practitioner, who is obliged to do some operations on the ear.

Genito-Urinary Diagnosis and Therapy. By DR. ERNST PORTNER, Berlin, Germany. Translated and Edited by BRANSFORD LEWIS, M. D. Illustrated. \$2.50. (St. Louis: C. V. Mosby Company, 1913.)

Though the word diagnosis enters into the title of this book, yet in the preface the author distinctly states that he takes it for granted that the diagnosis of the subject is understood, and, in fact he writes but little on diagnosis. As a therapy, students especially, and the general practitioner will find this a useful work. The detail of major operations is not generally given, the author simply indicating when an operation is necessary, so that the book must be recognized to have distinct limitations, but so far as Portner undertakes to instruct, his advice is good and sensible. The illustrations are ordinary, and those for the operation of circumcision very poor. On page 176 the last line of the second paragraph is omitted—four words being repeated which occur properly as printed in the second line below.

The Doctor in Court. By EDWIN VALENTINE MITCHELL, LL. B. \$1. (New York: Rebman Company, 1913.)

This is a serviceable small volume for the physician. From it he can learn readily what the burdens and responsibilities of his profession are as looked at from the legal point of view. It does not deal in the ordinary sense of the word with medico-legal questions, but "is an attempt to put briefly . . . the general principles of the law relating to the medical profession and the reason for those principles." Mr. Mitchell takes up the questions of professional evidence, the contract, civil and criminal responsibility of the profession, remuneration, confidential communications and qualifications. The busy practitioner is often in a quandry as to what are his rights on many of these points, and he will find here a clear exposition of the general status of the law. All the relations, discussed by the author, are important, and the book, because of its brevity and simplicity, will appeal to a large number of readers.

The Narcotic Drug Diseases and Allied Ailments. By GEO. E. PETTEY, M. D. \$5. (Philadelphia: F. A. Davis Company, 1913.)

On the belief that "the essential pathology of narcotic-drug addiction (disease) is a toxæmia, a toxæmia of drug, auto, and intestinal origin," which can be cured principally by a purging of the system of these poisons, the author has built up a large book of five hundred pages. We wish that others had had as much success as the author in curing these unfortunates addicted to these habits, but there seems to be a very general opinion that this class of patients is a most difficult one to cure permanently—relapses being exceedingly numerous. Doctors, who treat the drug habitués, will be glad of this opportunity to study Dr. Petty's theory and system more closely.

George Crocker Special Research Fund: Studies in Cancer and Allied Subjects. Vols. I and III. \$5 per volume. New York: Columbia University Press, 1913.)

The first volume is devoted entirely to a review of "The Study of Experimental Cancer," by Dr. William H. Woglom, which will be of great service to all students of the cancer problem, as "no extensive review of the more recent experimental investigation of cancer was available." A review of the chemical and bacteriological studies of cancer have not been included by the author.

Volume III contains a large number of papers from the departments of zoology, surgery, clinical pathology and biological chemistry of Columbia University on subjects which are fundamental to a proper understanding of the problems involved in the study

of cancer. It is fortunate for specialists that these very handsome books are sold at such a comparatively cheap price. Both volumes contain numerous fine illustrations.

The Microtome's Vade-Mecum. By ARTHUR BOLLES LEE. Seventh Edition. \$4. (Philadelphia: P. Blakiston's Son & Co., 1913.)

This is a book every microscopical laboratory worker will find most useful to have close at hand. Lee has complied practically all the useful methods of staining and preparing microscopical specimens, and keeps his well-known work up-to-date by including all the newer means that have proved themselves of value. It is excellently well arranged and has a good index so that its users can readily find what they need, and if they so desire look up the original papers in which the methods are described.

International Clinics. Vol. III. Twenty-third Series. 1913. \$2. (Philadelphia and London: J. B. Lippincott Company.)

The largest clinic is by Gwyn of Philadelphia on the "Treatment of Pneumonia"; it is an interesting paper as showing the results achieved with different forms of treatment during one winter at the Philadelphia Hospital.

Daniel of London writes at length on "Gastro-Intestinal Toxæmia," and Abrams of San Francisco writes on the value of the concussion of the seventh cervical spine for stimulating the heart-reflex, what he calls his method of "vertebral reflex therapy."

All the clinics treat of subjects of perpetual interest from one point or another to the physician and surgeon, and introduce to many readers new methods of treatment which may help to make their practice better if carefully studied.

Dict in Health and Disease. By JULIUS FRIEDENWALD, M. D., and JOHN RUHRÄH, M. D. Fourth Edition, Thoroughly Revised and Enlarged. \$4. (Philadelphia and London: W. B. Saunders Company, 1913.)

This is the most helpful book on the subject in English for the general practitioner and student, and can be warmly commended. The new edition is evidence of its wide and well-deserved popularity. It is dedicated to Sir William Osler, and its fitting place on the bookshelf, is next to the latter's "Practice of Medicine."

Obstetrics for Nurses. By JOSEPH B. DELEE, M. D. Fourth Edition, Thoroughly Revised. \$2.50. (Philadelphia and London: W. B. Saunders Company, 1913.)

It is evident that this work has found favor with nurses or it would not appear in a fresh edition; but for them it seems to us too long and too detailed in parts, while for students although not primarily written, yet considered by the author as valuable for them, the book is insufficient. It is a pity that both the author and publishers show so little taste in the illustrations; even in a medical work to open on such a frontispiece as is here found is not artistic, and others of the drawings might have been made more comely.

Essentials of Prescription Writing. By CARY EGGLESTON, M. D. \$1. (Philadelphia and London: W. B. Saunders Company, 1913.)

The "essentials" are here compressed into very brief space, too brief for the book to be really useful except to those who desire only the merest outline. It is not nearly so good as Mann's small work on the same subject which has long been the standard, and is short enough.

Gray's Anatomy: Revised and Recedited. By ROBERT HOWDEN, M. B., etc. Illustrated. (Philadelphia and New York: Lea & Febiger, 1913.)

There is probably no American or English text-book in any branch of medicine so deservedly popular as Gray's Anatomy, or

one that has passed through so many editions. This is a new American from the eighteenth English Edition. The essential alteration adopted by Howden is the use, practically throughout, of the B. N. A. He has added some new illustrations, and made some changes in the arrangements of the paragraphs on Surface Anatomy. It is to be hoped that until some better anatomy is written, which is not a likely probability, that Gray's will remain henceforth without further changes. There is a danger that more changes would injure it. His anatomy was a masterpiece, and to tamper with such a work is likely to do it harm. It would be interesting to know what opinion Gray would have of his work in its present form. The adoption of the B. N. A. is undoubtedly to be commended. The other changes will or will not be approved in accord with the individual reader's feelings.

Diagnosis in the Office and at the Bedside. By HOBART AMORY HARE, M. D. New (7th) edition, thoroughly revised and rewritten. Illustrated. \$4. (Philadelphia and New York: Lea & Febiger, 1914.)

Under a somewhat altered title Hare's well-known work appears for the seventh time, somewhat abbreviated because practically all laboratory methods of diagnosis purposely have been omitted. The book has been appreciated in the past, and will continue to be in the future, for the author's method of presentation is one that is attractive to many students. This "Diagnosis" is a useful clinical guide.

Treatment of Internal Diseases for Physicians and Students. By PROF. NORBERT ORTNER. Edited, with additions, by NATHANIEL BOWDITCH POTTER, M. D. Translated by FREDERIC H. BARTLETT, M. D. \$5. (Philadelphia and London: J. B. Lippincott Company, 1913.)

Although it does not appear on the title page, yet this is the second English edition of this work, from the fifth German, which has been so much altered by the author, that the new English issue is materially different from its predecessor. The chapters on children's diseases have been entirely rewritten, and the English scale of measures is supplied alongside of the French, and Fahrenheit scale is used to record the temperatures noted in this book. The editor has added many notes as well as a chapter on neurasthenia. This is a work which students and general practitioners will find an excellent guide to the treatment of internal diseases. It is safe and sound, and sufficient drug therapy is indicated to meet the needs of any practitioner.

The Physician's Visiting List for 1914. \$1.25. (Philadelphia: P. Blakiston's Son & Co.)

This useful note-book, well suited in size and shape to be carried in the pocket, is always timely in appearance. The country practitioner will find it of service, as he drives from one patient to another, for all sorts of notes, and for reference, as it contains numerous tables, which are not always at one's fingers' ends.

Diagnosis of Bacteria and Blood-Parasites. By E. P. MINETT, M. D. Second Edition. \$1. (New York: Hoeber, 1913.)

There should be no call for such a work as this; it is too small to be of any real value to an honest student of this subject. There is only one illustration and that a wretched one of the malarial organism.

Radium and Cancer. By LOUIS WICKHAM and PAUL DEGRAIS. Translated by A. and A. G. BATEMAN, M. D. \$1.25. (New York: Hoeber, 1913.)

This brief presentation of the effects of radium on various forms of cancer, illustrated by many photographs, is a helpful manual for the radiologist. Dr. Wickham lectured in this country several years ago, and explained what could be accomplished with radium when skillfully applied in various ways in the treatment of can-

cer. In "Radium and Cancer" he shows very remarkable results he and his confrère have obtained by their brilliant manipulation of this dangerous remedy.

Modern Problems of Biology. By CHARLES SEDGWICK MINOT, LL. D., etc. Illustrated. \$1.25. (Philadelphia: P. Blakiston's Son & Co., 1913.)

Incomplete, since they are presented in a condensed form, these lectures, delivered at the University of Jena by Dr. Minot, offer much of living interest to the reader, whether scientist or layman. Who is not interested in the questions of immortality, death, and sex even when considered from a purely scientific point of view? These are a few of the vital problems of biology which Minot discusses lucidly and learnedly.

A Manual of Surgical Treatment. By SIR W. WATSON CHEYNE, Bart., F. R. S., etc., and F. F. BURGHARD, F. R. C. S. In Five Volumes. (Philadelphia and New York: Lea & Febiger, 1913.)

The fifth and last volume of this excellent system is of the same high quality as its predecessors. It is a valuable work and one which will appeal to a large body of surgeons. It is not too bulky, and yet covers the general field of work in a very comprehensive and satisfactory manner. The original authors have been ably aided by their assistants Drs. Legg and Edmunds. The publishers are to be complimented on this handsome product of their press.

Cancer of the Breast. By CHARLES BANETT LOCKWOOD, F. R. C. S. (Eng.). \$3. (London: Henry Frowde and Hodder & Stoughton, 1913.)

Quite from his own experience the author has composed this book, which, due to the introduction of case histories in the same type as the body of the text, is from one-third to one-half larger than need be. The author's results compare well with those of most operators; there are a few, perhaps, who could show a greater list of recoveries. The work is of interest as the expression of one able surgeon's thoughts and results in a most important branch of his art.

Artificial Parthenogenesis and Fertilization. By JACQUES LOEB. \$2.50. (The University of Chicago Press, 1913.)

It is somewhat strange that this work appeared originally in German, about four years ago, and that American students have had to wait so long for an English edition. In the meantime, however, Loeb has had the opportunity to add to his first publication, so that in its new form the reader finds the latest results of the author's most brilliant and interesting discoveries. Loeb's work has long since been universally admired and praised by all capable of following his investigations, and this volume shows the originality of his thought, and skill in investigating abstruse and difficult problems. The book is a real addition to knowledge and is of fundamental importance to various branches of science.

Year-Book of the Pilcher Hospital. 145 Gates Avenue, Brooklyn, N. Y., 1913.

The appearance of this third volume is modest and most attractive. The Pilchers are to be complimented on its publication, a noteworthy index of the work done by these surgeons in their small private hospital. The papers included cover a wide field of surgery, and discuss topics of interest to all surgeons. It is an excellent proof of the general advance in medicine that three surgeons working together should issue a report of their work annually.

Surgical Experiences in South Africa: 1899-1900. By GEORGE HENRY MAKINS, C. B., F. R. C. S. Second Edition. \$3.75. (London: Henry Frowde and Hodder & Stoughton, 1913.)

The value of this work is very distinct for the army surgeon. Even with the limits of the writer's experience, the book will, as it has already, commend itself to careful students of war problems. Of especial interest are the late notes on the patients, whom Mr. Makins was able to follow up on his return from Africa to England. The work is well illustrated, and is an important addition to the comparatively small number of volumes dealing with surgery on the battlefield.

The Modern Treatment of Nervous and Mental Diseases. By eminent American and British authors. Edited by WILLIAM A. WHITE, M. D., Superintendent of the Government Hospital for the Insane, Washington, D. C., and SMITH ELY JELLIFFE, A. M., M. D., Ph. D., Adjunct Professor of Diseases of the Mind and Nervous System in the Post Graduate Medical School and Hospital. Two octavo volumes, containing about 900 pages each, illustrated. Per volume, cloth, \$6. (Philadelphia and New York: Lea & Febiger, 1913.)

Had psychiatry not taken such a prominent rôle of late in the study of medicine there would hardly have been a call for this system, but happily both physicians and the laity at last have begun to have their eyes opened to the part that the brain plays in disease as well as in health, and the nervous and mental diseases as also many other conditions of life have henceforth to be studied from an entirely new point of view. Under these conditions the public, and we use the word advisedly, is fortunate to have such a comprehensive and able exposition of the treatment of these diseases as is to be found in these two large volumes. Parts of the first volume will interest the social workers, lawyers, and public officials, as well as physicians, while the second volume is more purely medical. It is a pity that the general papers should be buried, so to speak, where those who are not doctors, but who are anxious to inform themselves on the questions treated, will hardly be likely to find them. There are chapters on education, sexual problems, delinquency and crime, immigration, alcoholism, etc., some written by non-medical experts, which are discussed in a manner not too scientific to be readily understood by a person of intelligence. Today these social questions are being widely handled in newspapers and journals, often by those who are quite incompetent to write intelligently about them, but here we have authoritative expositions of these difficult problems. Most physicians also are ignorant about these matters, and they will do well to acquaint themselves with the modern views of treatment as presented in this treatise by leading American and English neurologists and psychiatrists. The editors are to be warmly congratulated on having accomplished their task so successfully—the chapters are well balanced, and the merit of the volumes is high. Many of the chapters close with long bibliographies, there is a good index to each volume, and the illustrations are well chosen and not too numerous.

Gonorrhea in Women. Its Pathology, Symptomatology, Diagnosis, and Treatment: Together with a review of the rare varieties of the disease which occur in men, women and children. By CHARLES C. NORRIS, M. D. 521 pages. Illustrated. \$6. (Philadelphia and London: W. B. Saunders Company, 1913.)

The size of this volume is directly due to the Index Medicus and the Surgeon-General's Catalogue, and this is the only possible ground of complaint that can be brought against these two most valuable and splendid publications—they make it possible to review the medical literature of all countries so that authors can compile, on any common subject, over-exhaustive and exhausting

works, for few writers have the proper sense of proportion. Dr. Norris has used 2300 references culled from 20,000 found catalogued only in the last ten years. Had he written a treatise on this subject from his own experience it would have had a more distinct value. As a comprehensive work it can be recommended to all who have time to read it; even the layman will find in it chapters of interest, touching on gonorrhœa from a sociological point of view—one of its sides which, within a few years, has assumed a much greater importance than it formerly held. The disease, with its rarer complications, is well presented, so that also as a work of reference this book has value; but its size, cost, and weight (for which the publishers are responsible) will obstruct its merits being generally recognized and appreciated.

Studies Concerning Glycosuria and Diabetes. By FREDERICK M. ALLEN, M. D. (Cambridge: Harvard University Press.)

In a volume of over 1100 pages, with a bibliography of nearly 70 pages, but no index, a most unfortunate lack, Dr. Allen presents the results of three years of study on these conditions. The work is not for students but for specialists and laboratory workers; it covers, however, a ground which has not been before really elaborated in any work in English, so that the need of such a volume and a smaller, more practical one is undeniable. As a result of his investigations the author believes "that the cure of diabetes is now a feasible experimental problem." We trust that the work of others may prove it so, and that Dr. Allen may have the pleasure and satisfaction of seeing his studies become the foundation of the proper treatment of these most troublesome conditions. The solution of this problem depends more on the laboratory worker than the clinician, and its complexity is shown by the difficulty of its solution in spite of all who are working to solve it. A study like Dr. Allen's, even if it is not confirmed, is a valuable piece of work from the negative side, and so, although the author may be disappointed in finding that his results are not so important as he had hoped, he may find consolation in the thought that he is none the less helping others to find the right path.

The Catarrhal and Suppurative Diseases of the Accessory Sinuses of the Nose. By ROSS HALL SKILLERN, M. D. \$5. (Philadelphia and London: J. B. Lippincott Company, 1913.)

This book of Dr. Skillern's was gotten together for the use of students, and is an admirable work for this purpose. It is well illustrated with original drawings which clearly bring out the points they are intended to show.

The anatomical descriptions are well written and concise, and not merely a re-hash of the material contained in the works on general anatomy.

The most commendable thing about this book, however, is the numerous references to the original articles. They are given at the foot of each page, and include all the best and most recent German, French and English publications on this subject. This feature alone makes it the most valuable text and reference book on this subject that we have as yet seen in the English language.

It is much to be regretted, however, that the author does not lay more stress on the relation of the infections of the accessory sinuses to general systemic disorders and diseases.

Only a small percentage of medical students become "specialists" in the diseases of the nose and throat, but each and every one should know that gastro-intestinal disturbances may result from the swallowing of pus; that anæmia, arthritis and nephritis may all have their origin in an unsuspected chronic infection of one of the accessory sinuses; and that many of the disturbances of the optic and oculo-motor nerves are secondary to obscure infections in the nose.

Pathology: A Manual for Teachers and Students. By W. J. COUNCILMAN, M. D. (Boston: W. M. Leonard, 1912.)

Professor Councilman has introduced several new features in this manual of pathology, most conspicuous being the absence of any illustration, and the presence of several blank pages following each chapter. Illustrations were omitted because the author feels they too often represent carefully selected areas for the illustration of a point, more commonly an individual interpretation. The blank pages are inserted that the student may make personal notes and drawings of objects studied, thereby helping create his own text-book.

Many protocols of autopsies are included presenting typical morbid processes assisting the student to correlate the lesions as a disease of an organism rather than of a single organ.

The infectious diseases and special pathology of organs are considered with more fullness than subjects which seem to the author to illustrate principles of less wide application.

After most chapters suggestions are given which serve as a guide to the experimental production of lesions considered.

The manual is of convenient size for class and laboratory work, consisting of 393 pages exclusive of blank pages.

It will be found a valuable book for the student in correlating and preserving his observations.

Diagnosis of the Malignant Tumors of the Abnormal Viscera. By PROFESSOR RUDOLPH SCHMIDT. Authorized English Version by JOSEPH BURKE, M. D. \$4. (New York: Rebman Company, 1913.)

The work is divided into three parts—a general, special and case histories. In the special part the author considers carcinoma of the stomach, large intestine, liver, gall bladder, pancreas, malignant tumors of the kidney, and atypical malignant abdominal growths. Throughout this useful guide, Dr. Schmidt tries "to emphasize the most important factors of suspicion," as well as "the symptoms which appear first"; and by the use of case histories adds much to the value of his book, since he is hereby able to trace the history of the patient through the hands of physician, surgeon, and pathologist. For a young clinician the work affords much that is of real interest and help.

Problems of Genetics. By WILLIAM BATESON, F. R. S. Illustrated. \$4. (New Haven: Yale University Press, 1913.)

A most interesting series of lectures, presented under the Silliman Memorial foundation, on species and variety. It is not adopted to the general reader, but specialists in biology will value highly Professor Bateson's presentation of the subject. The problems of genetics are many and varied, and their solution is extremely difficult, but of vital importance to physicians, and it is a pity that there are so few medical men who are able to follow and comprehend such a work as this, which demands a wider range of scientific knowledge than most of them have.

A Text-Book of Biology. For Students in Medical, Technical and General Courses. By WILLIAM MARTIN SMALLWOOD, Ph. D. Illustrated. \$2.75. (Philadelphia and New York: Lea & Febiger, 1913.)

Dr. Smallwood's text-book will doubtless be popular, it is abundantly and elaborately illustrated, is not too long, and gives the medical student such information as he most needs and a good foundation to build upon. The author shows the practical connection of biology to medicine, which is required to interest the student. Had medical students, as a class, a better grounding in biology they would be more capable physicians, but this un-

fortunately they do not see until too late, and so lose something which is very essential to their development of intelligence and culture.

Modern Medicine: Its Theory and Practice. In original contributions by American and foreign authors. Edited by SIR WILLIAM OSLER, Bart., M. D., F. R. S., and THOMAS McCRAE, M. D. Second Edition Thoroughly Revised. (Philadelphia: Lea & Febiger, 1913.)

Vol. 1.—Bacterial diseases; diseases of doubtful or unknown etiology, non-bacterial fungus infections, the mycoses.

The appearance of the first volume of the new edition of Osler's *Modern Medicine* six years after the beginning of the first edition is evidence enough that this work has been and is still in demand.

The new edition is to be condensed into five, instead of seven, volumes and its price proportionally reduced, so that it may have a wider distribution among the English speaking profession. In physical appearance the new volume is a very great improvement on the original edition; the page is larger with better type and paper, and the illustrations are quite in a different class from the very poor productions in the first edition. The number of pages in the volume is also considerably increased, and, last but not least, we have a much more acceptable binding.

The subject matter in the first volume covers a good part of volumes I and II of the earlier text, revised to date with the addition or expansion of some subjects such as the articles on pellagra and trypanosomiasis which have assumed a new importance in the last few years.

There will be those who regret the elimination of the historical paragraphs and, to a large extent, of the bibliographies. In fact it is one of the most important functions of a system to contain accurate collections of the literature to date.

Be this as it may, however, there is no doubt that the work is one of the best systems in English and will meet the demands of the greater part of the profession fully and so justify the success it has had and will continue to enjoy.

Der Primäre Lungenherd bei der Tuberculose der Kinder. Von Dr. ANTON GHON. \$2.15. (Berlin und Wien: Urban & Schwarzenberg, 1912.)

In this monograph Ghon discusses fully and with care a rich pathological material, described with sufficient detail. The investigation is directed mainly upon the relations of tuberculous pulmonary foci to the adjacent tuberculous lymph nodes. Ghon brings extremely strong evidence for the view that the pulmonary focus is always the primary one. The involvement of the lymphatic system can always be shown to be secondary although the demonstration is at times accomplished only by the most painstaking dissection. This is confirmatory of the work of Küss and Albrecht, although many clinicians still hold that the tracheo-bronchial lymph nodes are first infected, and the lungs thereafter, through the nodes, by retrogression. Such a clinical opinion however now seems unreasonable. As regards the origin of the pulmonary focus, Ghon holds decidedly to an aerogenous route. He believes also on the basis of his material, that even where the striking tuberculous foci are elsewhere than in the lungs, yet nearly always, even in these cases, it is through the lungs that the invasion of the tubercle bacillus has occurred. S. W.

Mind and Health: With an Examination of some Systems of Divine Healing. By EDWARD E. WEAVER, Ph. D. (New York: The Macmillan Company, 1913.)

A plea is entered for the use of psychotherapy by religious bodies; as it is believed that one of the recognized offices of religion is to minister to all the needs of man. Instances are given of the failure of medical men, and occasions are cited where the minister,

after engaging in prayer with the patient has effected a cure. Those religious workers who employ psychotherapy are warned and encouraged to acquire a knowledge of its scientific principles, its application, and its limitation. It might have been well to tell them that they should have a thorough medical training, because otherwise they would not know with what they were dealing, and consequently by their intervention would probably do more harm than good.

The book is a very pretentious one, and has little to recommend it. The author is much more at home in the chapters dealing with Christian Science, the Emanuel Movement, and Divine Healing, than he is when he attempts to discuss psychotherapy.

Freud's Theories of the Neuroses. By DR. EDWARD HITSCHMANN. Translated by C. R. PAYNE. Journal of Nervous and Mental Diseases. Monograph Series, No. 17. (New York, 1913.)

In his introduction, Dr. Ernest Jones explains how in this volume an attempt has been made to present a concise synthetic review of Freudian theories. Such a presentation is exceedingly timely and valuable, and has been well performed both by the author and the translator. Freud's theories were at first confined to the neuroses, but their scope has now been so enlarged as to include normal dream life, wit, the development and variation of the instinct of sex, and still more recently criminality, certain psychoses, sexual perversions, and the source of religious, mythological, and superstitious beliefs.

It is pointed out how universal opposition has been raised against the Freudian doctrines, because of the disclosure of an unfailing sexual etiology. It is shown how both healthy and neurotic individuals are inclined to deny the paramount importance of sexuality, the healthy, because for them it constitutes no problem; the others because of their unconscious need to spread a veil over their own weakness.

Under the term neuroses, are included neurasthenia, anxiety, neurosis, hysteria, and compulsion, or obsessional neurosis. Neurasthenia and anxiety neurosis are called the true neuroses, because their cause lies in the present abnormal condition of the sexual function; whereas, hysteria and the obsessional neurosis are called "Psycho neuroses," because in these last the causative factor is in early childhood.

A good detailed description is given of these various states. Dreams are fully discussed, and other chapters deal with the Psycho-analytic Method of Investigation and Treatment, the General Prophylaxis of the Neuroses, and the Application of Psycho-analysis.

This volume is a valuable addition to this excellent monograph series, even although it is somewhat confounding at the present day to find such a statement as "the entire sexual abstinence before marriage is not to be generally recommended, let alone demanded, since it can lead in many cases to definite incapacity for work, and indeed directly to a neurosis."

D. K. HENDERSON.

The Surgical Clinics of John B. Murphy, M. D. Vol. II. Nos. IV and V. (August and October, 1913.) Illustrated. Published Bi-Monthly. \$8. (Philadelphia and London: W. B. Saunders Company, 1913.)

These numbers with their numerous illustrations differ in no essential way from their predecessors; the usual variety of surgical topics is discussed by Dr. Murphy in his breezy style. The clinics differ much in nature and importance. There is an excellent series of X-ray photographs of the blood supply in and around joints, made from injection preparations of a cadaver. Murphy's success with vaccines seems exceptional; many surgeons fail to secure the results he has obtained with them, and have less confidence in their value.

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A CLINICAL METHOD FOR STUDYING TITRATABLE ALKALINITY OF THE BLOOD AND ITS APPLICATION TO ACIDOSIS.

By ANDREW WATSON SELLARDS,
Assistant Resident Physician, The Johns Hopkins Hospital.
(From the Chemical Division of the Medical Clinic.)

In the investigation of the extremely varied properties and functions of the blood considerable attention has been directed toward the chemical analysis of its fundamental constituents. Satisfactory methods have been developed for the qualitative and quantitative estimation, not only of many of the common constituents, but also for some of the substances which occur in relatively minute amounts. However, the determination of one of the fundamental characteristics of the blood, namely, its chemical reaction, is very unsatisfactory. A variety of distinctly different principles have been utilized in the development of methods for studying the reaction of the blood. These methods, however, have not only failed to afford the information which is required clinically, but they are also unsuitable from an experimental standpoint.

Inasmuch as the expression, "the reaction of the blood," has come to be used in two senses, a brief discussion of term is advisable. In its strict sense, the reaction of the blood depends upon the physico-chemical balance between the hydrogen and hydroxyl ions which it contains. In this sense the blood is hardly more alkaline than distilled water. More loosely, the reaction of the blood was formerly stated in terms of its behavior toward indicators and its ability to neutralize acids

or bases. Although normal blood serum reacts as an acid toward a few indicators, notably phenolphthalein, yet it is definitely alkaline toward the majority of the common indicators and, since the alkaline reaction to these indicators can be maintained even after the addition of small amounts of acid, the blood is commonly spoken of as an alkaline fluid. From these considerations it will be seen that, although the physico-chemical measurements show the hydroxyl ion content of the blood to be very low, yet the blood contains a moderate quantity of substances which can readily yield hydroxyl ions upon the introduction of the hydrogen ion of an acid. Thus it is seen that two distinct interpretations have arisen for the term "reaction of the blood." In the present paper this term will be used in its physico-chemical sense to indicate the balance between hydrogen and hydroxyl ions and the behavior of the blood with indicators toward acids and bases will be designated as the titratable alkalinity. The question at once arises as to the relative importance in biological work of these two factors, namely, (1) the hydroxyl ion content of the blood, and (2) its titratable alkalinity. It has been shown by Henderson¹

¹Henderson: Am. Jour. Physiol., 1908, XXI, 427. See also Palmer and Henderson, Arch. Int. Med., 1913, XII, 153.

that the hydroxyl ion content of the blood varies but slightly, even under extreme pathologic conditions. This relatively constant value of the hydroxyl ion concentration is maintained, in part at least, at the expense of the titratable alkalinity. However, the detection of changes in the titratable alkalinity is difficult and unsatisfactory. The purpose of the present paper is to consider a method for detecting such changes and its application to clinical conditions, especially to acidosis. There are a variety of conditions in which the possibility of an acidosis has been suggested, more especially in certain of the nephropathies and anæmias, in eclampsia, and other complications of pregnancy and in several of the diseases of children, as in rickets and in the gastrointestinal disturbances.² Instead of examining for certain specific acids in each of these conditions, it would be much more satisfactory if a method of general application could be evolved which would not require the isolation and recognition of the acid in question. The determination of the tolerance to sodium bicarbonate affords such a method with the reservation, however, that the effect of renal lesions on the validity of this procedure has not been determined. Any methods for the detection of acidosis which depend upon the examination of the urine, may readily be inapplicable in the presence of renal disease, and, unfortunately, many of the conditions in which acidosis is suspected are complicated by disturbances of renal function.

Of the methods which have been proposed for determining the titratable alkalinity we need not consider the indirect procedures, such as the determination of the carbon dioxide content or the changes in the spectrum upon the addition of acid. Direct titration with some of the ordinary indicators has given the most suggestive results. As a type of this method we may consider the titration of blood serum against a standard acid with one of the azo dyes as an indicator. This group of indicators is extremely sensitive to alkalis, and apparently the underlying object in the use of them is to measure the full value of the titratable alkalinity. One of the principal objections to the procedure is that the end-point is extremely unsatisfactory. The protein of the serum is largely responsible for the interference with the end-point, but the removal of the protein would remove one of the important sources of titratable alkalinity. Furthermore, the maximal differences that are observed between normal and pathologic sera are without any striking significance. This necessitates the measurement, under unfavorable conditions, of small differences in the quantity of acid required for neutralization.

To obviate the difficulties of the titration methods it would seem desirable to develop a purely qualitative method in which all normal sera would react distinctly alkaline, whereas the pathologic sera would be distinctly acid to a given indicator. In the attempt to obtain such a result, the following departures from the usual titration methods were considered:

1. The selection of an indicator to which the serum of all normal individuals is acid, depending upon the conversion of the acid carbonates of the blood to normal carbonates in order

to obtain an alkaline reaction in normal individuals. The variation in the reaction of the blood toward different indicators is due, principally, to the sodium bicarbonate which it contains. This salt reacts as an acid to certain indicators, such as phenolphthalein, and as a base to others, notably methyl orange. However, on boiling, carbon dioxide is driven off and the normal carbonate is formed. The latter hydrolyzes in water and reacts as a base to all indicators. Thus, the content of sodium bicarbonate in normal blood is sufficient to explain why the serum reacts as an acid to phenolphthalein, but, after diluting with water and boiling, it will react sharply alkaline.

2. The removal of the interfering protein from the serum with the purpose of determining definite changes in the titratable alkalinity rather than the measurement of the total titratable alkalinity.

3. The substitution of another solvent for water to reduce the amount of hydrolysis and ionization. Before sodium carbonate can react with phenolphthalein, it must ionize and hydrolyze. These changes take place very readily in water, but by substituting some other solvent it might be possible to reduce these changes to such an extent that a trace of carbonate would give no reaction, whereas the amounts normally present in the serum would give a pronounced reaction.

From these considerations it is conceivable that conditions might be obtained in which all normal blood would be distinctly alkaline, whereas pathologic blood in which a definite diminution of sodium bicarbonate had occurred, might be distinctly acid under the same conditions. The basis of such a test would be essentially qualitative rather than quantitative. The feasibility of such a procedure has been tested in the following ways, namely:

1. Experiments with serum in vitro.
2. Experimental production of acidosis in lower animals.
3. Investigation of clinical conditions.

Selection and Preparation of an Indicator.—There have recently come into use a large number of indicators whose end-points change at varying concentrations of hydrogen and hydroxyl ions. Phenolphthalein is one of the most convenient of those which change to an acid reaction at a comparatively low concentration of hydrogen ions. The ordinary diacid preparation was employed for all qualitative work, using a $\frac{1}{2}\%$ solution in absolute alcohol. Later, for quantitative measurements, sufficient alkali was added to give a faint tinge of color to a large bulk of solution with the expectation that the colorless monosodium salt would change more readily to the red disodium salt than the acid itself. As a routine, 3 drops of either solution were employed; this indicator is such an extremely weak acid that accurate measurement proved to be unnecessary.

Removal of Protein and Selection of Solvent.—The removal of protein and the substitution of another solvent for water was combined in one step by precipitating the serum with alcohol. The removal of the protein avoids any interference with the end-point and at the same time removes a definite fraction of alkali-yielding substances which are probably fairly persistent, thus affording the possibility of obtaining a more

² See Ewing: Arch. Int. Med., 1908, II, 330.

sensitive test than could be secured with the aqueous dilutions of the whole serum. The removal of all traces of protein was not attempted, but practically complete removal was obtained by precipitation with absolute ethyl alcohol.

Experiments in Vitro.—The purpose of the tests in vitro was to determine whether the addition of minimal quantities of acid to serum could be detected by the use of phenolphthalein under conditions in which the titrations by the usual methods would not reveal the addition of the acid. To 1 cc. quantities of normal human serum increasing quantities of standard sulphuric acid were added. With the lower quantities of acid, sufficient water was added to make a final volume of 2 cc. of the mixture of acid and serum. The following observations were made on these specimens:

1. Reaction of the residue after incineration in platinum.
2. The reaction after diluting with water and boiling.
3. Precipitation of the protein with alcohol and the reaction of the alcoholic filtrate.

For the incineration in platinum the specimens were ashed at dull red heat. The residue was dissolved in water and the reaction tested to phenolphthalein. For the aqueous tests the mixture of serum and acid was diluted with about five parts of water and, after boiling freely for a minute, the reaction to phenolphthalein was tested. For the tests after removal of the proteins, 2 cc. quantities of the mixture of acid and serum were added, drop by drop, to 25 parts of absolute ethyl alcohol. The mixture was then shaken thoroughly and filtered. The filtrate, after the addition of phenolphthalein, and without any washing of the precipitate, was evaporated to dryness on a water bath.

The examination of a few specimens was sufficient to determine the characteristics of the reactions which were obtained under these conditions. The reactions with normal sera were essentially similar to the behavior of sodium hydroxide with phenolphthalein under the same conditions. The alcoholic filtrate upon concentration on a steam bath, rapidly took on a deep red color. This color was dependent upon the temperature of the solution, for upon rapidly cooling the solution the color faded markedly or disappeared completely. This change took place immediately before there was time for the absorption of carbon dioxide from the air, and was due apparently to a diminished dissociation with the lowering of the temperature. Upon evaporation to dryness the residue retained its red color for many hours. As a rule, six to eight hours heating on the steam bath were required to decolorize the residue. As the quantity of acid was increased, the residue, though red at first, rapidly became colorless on heating. With still further addition of acid, no color appeared at any stage of the evaporation, but the addition of water to the residue produced a red color. Lastly, those cases occurred in which no color was obtained during the evaporation or upon the addition of water to the residue. In some of these cases, however, the boiled aqueous dilution of the serum would give a distinct color with phenolphthalein.

Pure sodium hydroxide gave reactions with phenolphthalein which corresponded to the behavior of normal serum.

Traces of sodium hydroxide (0.5 to 0.1 cc. of N/200 solution) when added to 25 cc. of absolute alcohol gave no color upon evaporation to dryness. The residue upon dissolving in water became distinctly pink or red. The residue, after the evaporation of phenolphthalein with an aqueous solution of sodium hydroxide, retained its red color, often for as long as twenty-four hours on a steam bath. On heating in an air bath at 90° C. the pink color was almost completely discharged in two or three hours.

The results of the reactions with phenolphthalein have also been compared with the usual titration methods for blood serum. Of the various procedures, the use of standard acid, with one of the azo dyes, was selected since this is the most feasible for clinical purposes, and in the hands of some investigators it has given rather suggestive results. Many technical variations have been suggested in the application of this procedure. Of the azo dyes, dimethylamidoazobenzene (Töpfer's reagent) is recommended by Strouse.³ The principal advantage of the technique devised by Wright⁴ for the quantitative titration of serum with acids appears to lie in minimizing the quantity of serum which is required. Inasmuch as moderate quantities of serum were available in the present work, the titrations were carried out in the ordinary manner. The following routine applies to all the results with Töpfer's reagent which are recorded in this paper. One cubic centimeter of serum was diluted with water until the color of the serum was practically eliminated; usually about 100 to 200 cc. of water were required; 3 to 4 drops of a ½% solution of the indicator in 95% alcohol were used. The addition of N/10 hydrochloric acid was continued until the distinct yellow of the Töpfer's reagent, not only had deepened considerably in color, but until a definite pink shade appeared. So much acid was required to effect this change that there was no advantage in using a higher dilution than N/10. Indeed, in some instances, no end-point was obtained, but the addition of a relatively large proportion of acid effected only a very gradual change in color through all shades from yellow to red. It is understood, therefore, that the figures for Töpfer's reagent represent only approximations and for the most part do not represent a sharp end-point.

From these data (Table I) it is evident that the quantity of acid which is sufficient to produce a definite change in the reaction to phenolphthalein is much too small to be detected with any certainty in the titrations against Töpfer's reagent under corresponding conditions. Thus the end-point with Töpfer's reagent can hardly be determined to greater accuracy than 0.1 or 0.2 cc. when a N/10 solution is used. However, the addition of the equivalent of 0.1 to 0.2 cc. of N/10 acid to 1 cc. of serum could be detected very readily by the use of phenolphthalein.

Experimental Acidosis.—In the application of these tests to conditions occurring in the animal body, it is to be expected that the results would depend largely upon the compensatory processes of metabolism. The efficacy of these processes might vary widely; therefore, the reaction was first studied in ani-

³ Strouse: Johns Hopkins Hosp. Bull., 1908, XIX, 137.

⁴ Wright: Lancet, London, 1897, II, 719.

mals in order that it might be tested under conditions in which a simple definite acidosis of known etiology could be established. For this purpose acidosis was produced by the administration of mineral acid. Among the various possibilities of this experimental acidosis the two extreme effects that might be produced are: (1) the carbonates in the blood may diminish under the administration of acid, or (2) such a condition may

TABLE I.
ADDITION OF ACID TO SERUM IN VITRO.
FIRST SPECIMEN.

CC N/25 acid per cc. serum.	Behavior toward phenolphthalein.				
	After removal of protein.			1-10 dilution of whole se- rum in water.	Incinerated residue in water.
	In alcoholic solution.	Residue after evaporation.	In aqueous solution.		
None	Red	Red 7 hrs.	Red	Red	Red
0.05	Red	Red 1 hr.	Red
0.10	Red	Red 15 min.	Red	Red
0.15	Red	Red 15 min.	Red	Red
0.20	Red	Red 15 min.	Red	Red
0.25	No color	Red 5 min.	Red	Pink	Red
0.5	No color	No color	No color	Trace	Red

SECOND SPECIMEN.

None	Red	Red 6 hrs.	Red	Red
0.25	Red	Red 15 min.	Red	Pink
0.4	Red	Red 5 min.	Red	Red
0.45	Red	No color	Red	Pink
0.5	No color	No color	Pink	Pink
0.6	No color	No color	No color	No color	Red
0.7	No color	No color	No color	No color	Red
0.75	No color	No color	No color	No color	Red
1.0	No color	No color	No color	No color	Red
1.5	No color	Red

THIRD SPECIMEN.

0.25	Red	Red	Red	Red
0.5	No color	No color	No color	Pink
0.75	No color	No color	No color	No color

FOURTH SPECIMEN.

0.25	Red	Red	Red	Red
0.5	No color	No color	Trace	Red
0.75	No color	No color	No color	No color

be incompatible with life, a fatal effect resulting before the carbonates are appreciably reduced.

In case the carbonates do not diminish in the blood under the administration of acid, the question would arise as to the source of supply which could furnish sufficient carbonates or other alkali-yielding substances to meet the relatively large amounts of acid which it is possible to introduce into the body. It is readily conceivable that the blood might draw on the other tissues of the body for carbonates and death might result

from the exhaustion of these tissues before the blood itself was markedly depleted. On the other hand, in case a definite reduction in the bicarbonate content of the blood takes place, there are a number of compensatory mechanisms by which the respiratory processes may be continued.

Some experiments were undertaken to determine whether, upon the introduction of acid into the body, sufficient change takes place in the blood serum to give it a neutral or acid reaction to phenolphthalein. Hydrochloric acid was administered through a stomach tube to rabbits after the manner of the original experiments of Walther.⁵ A 10% solution in water of absolute hydrochloric acid was kept as a stock solution and this was diluted to 1/2% before use. Walther estimated that 0.9 gm. of hydrochloric acid per kilo per day was fatal for rabbits (approximately 25 cc. of a normal solution). For the production of an acute acidosis, I have used quantities of 0.5 gm. per day. In some experiments this was divided into two doses, one of which was given in the morning and the other in the afternoon.

For the examination of the serum with phenolphthalein the following routine was used throughout the remainder of the experiments described in this paper. The description is given in some detail, inasmuch as there are a number of minor factors which might definitely affect the results.

The serum was usually examined at the time of collection, especially in the important cases. In some instances it was stored in the refrigerator, but the examinations were always made within twenty-four hours after the time of collection. Absolute alcohol was chosen in preference to 95%, partly on account of its freedom from organic acids and also to reduce the amount of water in the reaction mixture to a minimum. In order to test its neutrality 0.1 cc. of N/200 sodium hydroxide was added to 25 cc. of alcohol, using 2 to 3 drops of phenolphthalein as indicator. The mixture was evaporated to dryness and the residue, on taking up in a few drops of water, gave a distinct color. For the incinerated specimens, a drop of serum was ashed at dull red heat in a platinum crucible. The residue was taken up in water and a few drops of phenolphthalein were added. The preparations with water were made in 1-10 dilution and boiled in a test tube over the free flame for one minute or more. In the case of normal sera a pink color appeared immediately upon the addition of phenolphthalein. In other cases it frequently happened that preparations which were colorless at first would develop a trace of color on standing for five to ten minutes. Such a behavior was somewhat unexpected, since phenolphthalein in aqueous solutions fades on cooling, owing to the absorption of carbon dioxide from the air. However, the preparations of normal serum in water also faded after several hours at room temperature.

High dilutions of normal sera in water, even 1 to 1000, usually gave a distinct color with phenolphthalein after boiling. As a rule, however, 1 part of serum was added to 10 parts of water. At this dilution, comparatively little precipitation of protein takes place on account of the alkali which is present. With a slight excess of acid, the solution remained compara-

⁵ Walther: Arch. f. exper. Path. u. Pharmacol., 1877, VII, 148.

tively clear on heating, but after approximate neutralization by small quantities of acid, abundant precipitation of protein occurred on heating on account of the lack of alkali for the formation of the soluble alkali albuminate. This precipitate occasionally interfered with the detection of faint traces of color, since a practically colorless solution would sometimes become faintly pink upon high dilution; the results could hardly be misleading, however, as the interference is so slight and the source of this interference depends upon the absence of alkali.

For the preparations with alcohol, 1 cc. of serum was added, drop by drop, to 25 cc. of absolute ethyl alcohol. The mixture was then shaken thoroughly and filtered into an evaporating dish. Perfectly dry apparatus, or apparatus washed with absolute alcohol, was used throughout in order to exclude all water from the mixture except that which is contained in the blood serum. Without washing the precipitate, 3 or 4 drops of phenolphthalein were added to the filtrate and evaporation to dryness was carried out on a steam bath (not over 100° C.). Only a minimum amount of steam was used during the evaporation in order to avoid, as far as possible, the excessive absorption of water vapor by the alcohol. The method of recording the results requires careful explanation. In the preparation of the experimental mixtures, many gradations of titratable alkalinity were produced. The variations in the behavior of phenolphthalein with bases in aqueous and in alcoholic solution fortunately offers the possibility of detecting some of the gradations. The alcoholic filtrate at the moment of going to dryness approaches an aqueous solution on account of the water added with the serum. In many cases the alcoholic solution remained colorless till this point was reached. In these cases the residue, however, instead of retaining its red color on the water bath for several hours, usually lost it within five to fifteen minutes.

In a series of examinations, where a great variety of transitional stages occur, it is obvious that there will be considerable variation in the minor details of the results that are obtained. However, it has not seemed necessary or advisable to attempt to describe all of these details; only the more significant changes have been noted. For many reasons it is not desirable to attempt to record shades of color. However, it is obviously necessary to distinguish between cases in which a personal equation does not come into consideration, as for example, in those cases where a pronounced red or a barely discernible trace of pink is obtained. In compiling the results in tabular form, the term "no color" is used. This refers only to the shades of red and pink. In many of these instances the dry residue was tinged with yellow, presumably on account of the lipoids of the serum. The absence of any pink color with phenolphthalein means, of course, that the solution was neutral or acid. Some of the most pronounced cases were titrated with N/200 sodium hydroxide. However, there was not a distinct difference between the amounts of hydroxide required for the test specimens and for a blank control. No further attempt was made to measure any acid which may have been present. It is not essential for the interpretation of the

results in the following tables, whether these colorless specimens are considered as neutral or faintly acid to phenolphthalein.

TABLE II.
EXPERIMENTAL ACIDOSIS IN RABBITS.
RABBIT I.

Day of experiment.	Grams HCl per kilo.	Interval between administration of acid and collection of blood.	Blood serum.				
			Alkalinity to Töpfer's in % N/1 solution.	Behavior toward phenolphthalein.			
				After removal of protein.			1-10 dilution of whole serum in water.
				In alcoholic solution.	Residue after evaporation.	In aqueous solution.	
1	None	0.7	Pink	Pink	Pink
	0.5	22 hrs.	0.7	No color	No color	No color	No color

RABBIT II.

1	None	0.8	No color	No color	Red	Red
	0.5	20 hrs.	0.7	No color	No color	No color	Pink

RABBIT III.

1	None	0.8	Red	Red 7 hrs.	Red
	0.5	20 hrs.	0.8	No color	No color	No color	Pink
2	0.5	26 hrs.	0.65	No color	No color	No color	No color

RABBIT IV.

1	None	0.7	Red	Red	Red
	0.25	6 hrs.	Red	Red	Red
	0.25	18 hrs.	Red	Red	Red
2	0.25	6 hrs.	0.75	Pink	Red	Red
	0.25	20 hrs.	0.7	No color	Red	Red

RABBIT V.

1	None	0.7	No color	No color	Red	Red
	0.25	5 hrs.	No color	No color	Red	Red
2	0.25	6 hrs.	0.7	No color	No color	No color	Pink
	0.25	15 hrs.	0.6	No color	No color	No color	Pink
3	0.5	20 hrs.	0.6	No color	No color	No color	Pink
	0.5	24 hrs.	0.65	No color	No color	No color	Pink
4	0.5	20 hrs.	0.6	No color	No color	No color	No color

Death two hours later.

RABBIT VI.

1	None	0.7	Pink	Pink	Red
	0.25	6 hrs.	No color	Pink	Red
	0.25	16 hrs.	0.7	No color	No color	No color	Pink
2	0.25	6 hrs.	No color	No color	No color	Pink
	0.25	18 hrs.	No color	No color	No color	No color

In this table, as in Table I, it will be seen that with increasing amounts of acid the reaction of the alkaline filtrate from the serum with phenolphthalein was frequently red in aqueous and colorless in alcoholic solution. With still further diminution in alkali the serum not only remained colorless after removal of the protein, but the aqueous dilutions of the serum did not color with phenolphthalein. This difference in aqueous

and alcoholic solution, and in the presence or absence of protein, offers the possibility of the ready detection of several different grades in the diminution of titratable alkalinity. These reactions with phenolphthalein may be listed tentatively as follows:

1. Persistence of red color in either alcoholic solution or dry residue for several hours.
2. Absence of color in alcoholic solution or transient appearance of color in the residue, but with good coloration in aqueous solution.
3. Total absence of color in alcoholic solution, in the residue on evaporation or after the addition of water, but with distinct color in the aqueous solution before removal of protein.
4. Total absence of color in all stages including the aqueous dilution without the removal of protein.

These stages would, of course, merge gradually into one another.

For convenience the sharper changes may be outlined as follows:

BEHAVIOR TOWARD PHENOLPHTHALEIN.

After removal of protein.			Without removal of protein.
In alcoholic solution.	Residue after evaporation.	In aqueous solution.	1-10 dilution of whole serum in water.
Alkaline	Alkaline	Alkaline	Alkaline
Alkaline	*	Alkaline	Alkaline
Neutral	Neutral	Alkaline	Alkaline
Neutral	Neutral	Neutral	Alkaline
Neutral	Neutral	Neutral	Neutral

* Color discharged on evaporating to dryness and heating for a few minutes.

From the results which are recorded in Table II, it is evident that a comparatively early grade of acidosis can be detected merely by the qualitative changes in the reaction of the alcoholic fraction of the serum toward phenolphthalein. These changes took place before the development of any clinical symptoms. Nevertheless, it was necessary to use rather large amounts of acid before sufficient change occurred in the blood to be detected by this method. Thus, Walther found that the introduction of 0.9 gm. of hydrochloric acid per kilo of body weight per day was fatal for rabbits. In this series it was necessary to introduce at least 0.5 gm. per kilo per day to obtain a definite effect, while in one case twice this quantity was necessary. In the advanced stages of this experimental acidosis the increasing frequency, and especially the increased depth of respiration served to compensate in part for the loss of alkali.

Walther observed that in experimental acidosis, death took place while the blood still remained slightly alkaline to litmus. The same holds true for all of the animals in this series. As regards phenolphthalein, however, the functions of the body may continue, for a limited time, although the serum after heating reacts neutral or acid to this indicator. The acid reaction to phenolphthalein of the alcoholic filtrate from the serum does not mean that the bicarbonates are absent from the serum itself, but rather that the fraction has disappeared

which is removed in the alcoholic filtrate. In some instances the heated aqueous dilution of the serum remained colorless with phenolphthalein. Such sera, however, are not wholly free from alkali-yielding substances; upon incineration of these specimens in platinum crucibles at low red heat, the residue when taken up in water reacted strongly alkaline to phenolphthalein, although the aqueous dilutions upon boiling were neutral or acid in reaction. Death occurred in all cases while the serum was still strongly alkaline to phenolphthalein after incineration.

The essential feature in this series of animals consists in the demonstration of definite changes in the reaction of the blood as a result of the effect of acid in vivo, as well as in vitro. Much larger quantities, however, were required to produce a corresponding effect in the animal body than in vitro. Thus, 1 to 2 cc. of N/100 acid per 1 cc. of blood serum in vitro produced an effect corresponding to the action in vivo of the equivalent of 1400 to 3000 cc. of N/100 acid per kilo of body weight. Of course, it is not possible that the acid which was introduced was distributed equally through the various tissues of the body and it is impossible to say just what proportion acted directly on the blood itself. It is evident, however, that relatively enormous quantities must be introduced into the body to produce the same effect upon the blood as are produced by minimal quantities acting in vitro.

In considering the clinical application of this method, it is hardly necessary to note that the experimental results were obtained under conditions which differ markedly from those arising spontaneously in man. In the first place, the introduction of a mineral acid by way of the alimentary tract is rather different from the formation of organic acids in the tissues and from defective elimination of acid salts by the kidneys. Moreover, it is well known that the herbivora react in a different manner from the carnivora toward the mineral acids, while it is supposed that the omnivora constitute a somewhat intermediate group.

In order to test the applicability of this method to clinical conditions, examinations were made in normal individuals, in cases of diabetic acidosis and unknown conditions where acidosis was suspected. Of the unknown conditions, attention was directed primarily toward the study of the nephropathies. In the series of diabetics some supplementary tests were carried out in order to facilitate the interpretation of the results obtained with phenolphthalein. The complete list is as follows:

I. Examination of the urine:

1. Determination of the ammonia coefficient.
2. Estimation of the acetone and β -oxybutyric acid, by Shaffer's method.⁶
3. Titration of the acidity by Folin's method.⁷

II. Examination of blood serum:

1. Titration with N/10 acid against Töpfer's reagent.
2. Behavior toward phenolphthalein.

⁶ Shaffer: J. Biol. Chem., 1908, V, 211.

⁷ Folin: Am. J. Physiol., 1903, IX, 265.

III. Determination of the effect of the ingestion or intravenous injection of sodium bicarbonate upon the reaction of the urine, *i. e.*, the tolerance to bicarbonate. The determination was carried out according to a principle which is strictly analogous to the work with sugars, *i. e.*, by estimating the amount which must be introduced into the body before it appears in the urine. Under certain conditions, when either sugars or carbonates are introduced into the body, a considerable quantity may be stored before any excretion takes place. It is recognized clearly that the cause and the manner of this storage may vary with different substances, and also for the same substances under different conditions. Throughout this paper the term "tolerance" is used in connection with bicarbonates without any reference to the explanatory factors which are involved. In the discussion of these cases it is extremely convenient to have a general term which may be used in unknown conditions without regard to the underlying explanation. For example, the expression, "tolerance to sugar," is used freely in the literature in a general sense, for it does not explain in detail the fate of sugar which is retained in the body. However, both the sugars and bicarbonates have certain important features in common. Thus, both of them may frequently be stored in the body essentially for use as such, *i. e.*, as carbohydrate and alkali. One of the striking differences between these two substances consists in the fact that relatively large amounts of sugar can be added to the diet of a normal person before any excretion takes place, whereas the addition of a little bicarbonate results in its prompt excretion in the urine. Thus, the differences between the two substances are, in part, only differences of degree. It would seem to the author to be appropriate to retain the term "tolerance" for use in a general sense with either alkalies or sugars. In case the explanation of the unknown cases is subsequently forthcoming, then it would be helpful, if possible, to select a term which would be explanatory for the case under consideration. Obviously, such a selection might prevent many difficulties. For example, in the case of the sugars, several factors may be involved in the explanation of a given case and, moreover, it is possible that the relative importance of these factors may vary from time to time in a given individual. In the case of bicarbonates, certainly no conclusive evidence has been offered which would enable one to decide upon the exact explanation of the cases. Consequently, it has seemed preferable to retain the term "tolerance" in a general sense, reserving the adoption of a specific term until the explanation of these cases is established.

Palmer and Henderson⁸ have recently proposed that the excretion of bicarbonate be studied by determining the concentration of the urine in hydrogen and hydroxyl ions. By the use of a series of indicators they conclude that any individuals who require more than 4 gm. of sodium bicarbonate are abnormal. Practically identical conclusions were reached simply by the use of litmus paper.⁹ The maximum amount of sodium bicarbonate was determined which is required to

change the reaction of the urine in any normal adult on a mixed diet, from acid to a neutral or alkaline reaction. It was found that 5 gm. was sufficient to produce a distinct change in practically all cases. The only exceptions to this which were found were two cases of neurosis in men. On investigation of these two cases it was found that at the time when they were tested the intake of water happened to be very limited, no exercise was permitted, and the appetite was extremely poor. A second dose of 5 gm. promptly produced an alkaline urine in each patient.

In the cases reported in this paper the reaction of the urine was tested to litmus paper. In those instances in which the reaction was not distinctly acid or alkaline the specimens were boiled thoroughly in order to convert any bicarbonate into the normal carbonate. The milder cases were tested by ingestion. Ten grams of sodium bicarbonate, mixed with water, were given by mouth through a glass tube, three times daily at intervals of six hours. For the intravenous injections a 4% or 5% solution in water was injected in quantities usually of 400 to 600 cc. at intervals of about eight hours. Appropriate precautions were taken to prevent excessive change in the solutions during sterilization.¹⁰ The bladder was emptied immediately before the ingestion or injection of bicarbonate and the reaction of the urine was tested before each repetition of the bicarbonate.

For the series of nephropathies the outline for the diabetic cases was changed slightly as follows:

I. Examination of the urine:

1. Determination of the ammonia coefficient.
2. Titration of the acidity of the urine by Folin's method.

II. Examination of the blood:

1. Titration of the serum against N/10 acid with Töpfer's reagent.
2. Behavior of the serum toward phenolphthalein.

III. Determination of the tolerance to sodium bicarbonate.

The determination of acetone and β -oxybutyric acid was omitted inasmuch as there is no reason to suspect a disturbance of carbohydrate or fat metabolism. A previous series of various types of renal disease showed no increase of these bodies in the urine.¹¹ Furthermore, as far as acetone is concerned under ordinary conditions, the qualitative tests when negative are sufficient to exclude any significant increase in its output.

In the series of control tests on normal individuals the only unknown factor is the determination of the behavior of normal serum toward phenolphthalein. The standard values for the other factors are so well established that they do not require repetition. The essential feature consists in the examination of the reaction of the alcoholic filtrate. In the examination of thirty normal cases it was found that the alcoholic filtrate upon concentrating gave a definite red color and, upon evaporating to dryness, this residue retained a distinct red or pink color. After several hours heating on a steam bath, the red color faded very gradually to a pale yellow. In some cases it did not dis-

⁸ Palmer and Henderson: Arch. Int. Med., 1913, XII, 153.

⁹ Sellards: Johns Hopkins Hosp. Bull., 1912, XXIII, 289.

¹⁰ Sellards: *loc. cit.*

¹¹ Sellards: *loc. cit.*

appear till after heating for six or eight hours, and in all cases there was a distinct pink visible for at least one hour. The change in color is so gradual and so slow in normal cases that it would be impracticable to set any exact time limits for its disappearance.

It would seem evident from these data that in all normal individuals the unheated alcoholic filtrate of the serum is neutral, or slightly acid, to phenolphthalein, and becomes alkaline upon heating. The individuals on which these tests were made included all ordinary ages, except the first decade of life. However, the subsequent tests on pathologic cases did not include any children. It seems most improbable that healthy children would show any marked variation from the adult in such fundamental characteristics as the alkalinity of the blood.

The first series of pathologic conditions which were tested was a group of seven diabetic patients, in four of whom (A, B, C and D) acidosis was present, while in three others (E, F and G) it was absent. Of the acidosis cases, two (C and D) were in an advanced stage with all the typical signs. The other two were in an earlier stage without clinical signs and without any definite increase in the excretion of acetone and related bodies, or of ammonia. The diagnosis of acidosis in these two cases was based on a well-marked increase in the tolerance to sodium bicarbonate (on intravenous injection). The behavior of their titratable alkalinity is shown in Table III.

TABLE III.
CASES OF DIABETES.

Case.	Urine.				Blood serum.				
	Acidity in % of N/1 solution.	NH ₃ coefficient.	Acetone, grams per liter.	β -Oxybutyric acid (grams per liter).	Tolerance to sodium bicarbonate (grams).	Alkalinity to Topfer's in % of N/1 solution.	Behavior toward phenolphthalein.		
							After removal of protein.		
							In alcoholic solution.	Residue after evaporation.	1-10 dilution of whole serum in water.
A	5.5	5.6	0.010	0.04	40	0.8	No color	No color	Pink
B	6.3	6.1	0.011	0.10	30	0.9	No color	No color	Red
C	4.5	11.7	2.20	3.3	50+	0.7	No color	No color	Faint pink
D	4.0	16.4	3.20	10.5	80+	0.8	No color	No color	Faint pink
E	3.5	6.0	0.100	0.26	5	0.8	Red	Red
F	4.0	5.7	0.135	0.38	10	0.9	Red	Red
G	3.0	3.4	0.412	0.21	10	0.8	Red	Red

In Table III the behavior of the serum toward phenolphthalein parallels the tolerance to sodium bicarbonate and bears no constant relation to any of the other factors recorded in the table. The parallelism between the behavior of the serum to phenolphthalein and the increase in the tolerance to bicarbonate in two patients (A and B) justifies the diagnosis of acidosis in these cases, if one considers acidosis to be an impoverishment of the body in bases. Moreover, the total daily output of ammonia averaged 0.4 to 0.5 gm. per day in each case and did not exceed the normal range of 0.4 to 0.6 gm. daily. We have, therefore, the existence of a definite acidosis without any appreciable increase in the relative or absolute excretion of ammonia. The behavior of the titratable alka-

linity was investigated in a group of nephropathies, selecting primarily those cases which show an increase in tolerance to sodium bicarbonate. The special object in view was to determine if the bicarbonate in these cases is retained on account of an acidosis or if it accumulates in the body on account of the inability of the kidney to excrete it.

There are a number of features which make it probable that this increased tolerance is to be explained by a deficit of bicarbonate in the body. Nevertheless, it is equally clear that no crucial evidence from any standpoint has been obtained for the determination of this question. One suggestive point is

TABLE IV.
CASES OF CHRONIC RENAL DISEASE.
IN UREMIA.

Case.	Urine.		Tolerance to sodium bi-carbonate (grams).	Alkalinity to Töp-fer's in % of N/1 solution.	Blood serum.			
	Acidity in % of N/1 solution.	NH ₃ coefficient.			Behavior toward phenolphthalein.			
					After removal of protein.			1-10 dilu-tion of whole serum in water.
					In alcoholic solution.	Residue after evap-oration.	In aqueous solution.	
A	3.5	3.0	160+	0.6	No color	No color	No color	No color
B	2.3	3.5	40+	0.9	No color	No color	Pink	Red
C	30+	0.6	No color	No color	No color	Pink
D	1.5	2.4	70	0.8	No color	No color	No color	No color
E	3.8	5.2	30	0.8	Pink	(1)	Red	Red
F	2.7	4.0	30	0.7	No color	No color	Pink	Pink
G	2.5	3.5	40	0.9	Pink	(1)	Red	Red

EXTREME CASES.

H	3.0	3.7	70 ²	0.6	No color	No color	Pink	Red
I	3.1	4.2	80 ²	0.8	No color	No color	No color	Red
J	2.5	2.6	70 ²	1.0	No color	No color	No color	Faint pink
K	2.0	8.7	80	0.8	No color	No color	Red	Red
L	2.0	11.6	40	0.7	No color	No color	Red	Red

OUTSPOKEN CASES.

M	4.0	7.1	30 ²	0.9	Red	(¹)	Red	Red
N	1.5	11.8	30 ²	1.0	Red	(¹)	Red	Red
O	2.7	3.0	20 ²	1.0	Red	(¹)	Red	Red
P	2.4	2.2	10 ²	0.8	Red	Red	Red
Q	1.8	4.0	10 ²	1.3	Red	Red	Red

¹ Colorless after five minutes. ² By ingestion.

that the urine of a nephritic which has been rendered alkaline by large doses of bicarbonate is, after the return of the acid reaction, rendered alkaline again by much smaller doses of bicarbonate than were necessary originally. It has been suggested that this fact constitutes an almost crucial test, proving the existence of acidosis.¹² It is obvious, however, that these results are open to another explanation. Thus, in the case of substances which are known to be retained in the body on account of renal lesions, it is characteristic that they are not

¹² Palmer and Henderson: *loc. cit.*

retained quantitatively when large amounts are introduced, but after a certain maximum has been reached excretion commences in the case of practically all substances. Consequently, when an acid reaction of the urine returns after the alkalinity following a massive injection of bicarbonate, it is obvious that the effect of an additional small dose of bicarbonate cannot form a crucial test for distinguishing between acidosis and retention. Table IV shows the behavior of 17 cases of renal disease, of the chronic diffuse type tested during a stage of good cardiac compensation.

In analyzing Table IV, the most significant feature is the general parallelism between the reaction of the blood to phenolphthalein and the tolerance to sodium bicarbonate. The following outline, compiled from Table IV, illustrates this feature:

BEHAVIOR OF SERUM TOWARD PHENOLPHTHALEIN.

No. of cases tested.	After removal of protein.			1-10 dilution of whole serum in water.	Range of tolerance to sodium bicarbonate (grams).
	In alcoholic solution.	Residue after evaporation.	In aqueous solution.		
2	Alkaline	Alkaline	Alkaline	Alkaline	10—
5	Alkaline	*	Alkaline	Alkaline	20 to 40
3	Neutral	Neutral	Alkaline	Alkaline	30 to 70
2	Neutral	Neutral	Neutral	Alkaline	70 to 80
2	Neutral	Neutral	Neutral	Neutral	70 to 160+

*Red color discharged in a few minutes by heat on water bath.

In this outline two cases (B and C, Table IV) are omitted, since the bicarbonate was discontinued in those patients presumably long before their tolerance was reached. Only the nephritic cases are included, as it is not unlikely that the relation between the reaction of the blood and the tolerance to sodium bicarbonate may vary according to the etiology of the acidosis. This possibility is suggested by the two fatal cases of diabetic acidosis (Table III, C and D), which did not show extreme changes in the blood, although the tests were made during the day on which these patients died. Case K, Table IV, is omitted because of the hepatic syphilis, since certain features of hepatic disease suggest the possibility of an acidosis. In this patient the tolerance is slightly higher than one might expect from the blood changes.

The gradations of changes in the blood as given in this outline can only be classified in a very general way. It is quite possible that, with accurate quantitative measurement of these changes, their parallelism to the alkali tolerance might be still more definite. This relationship between the titratable alkalinity and the increased tolerance to bases indicates that the latter is due, in part at least, to a deficit of the body in bases. It is rather more difficult to decide whether this deficit is the sole factor involved in the production of this increase in tolerance. It is quite conceivable that in addition to this deficit there may be an inability of the injured kidney to excrete bicarbonate. This question can be approached by studying the changes that take place in the blood upon the introduction of bicarbonate and their relation to the changes that take place

in the reaction of the urine. Thus, when the titratable alkalinity of the blood has been restored to normal, one would expect that the further introduction of bicarbonate would change the urine from an acid to an alkaline reaction unless there is suppression of the bicarbonate by the diseased kidney.

Some of the cases in Table IV, showing a high tolerance to sodium bicarbonate were studied to determine whether the changes in the blood and in the urine took place simultaneously. The results are given in Table V. In the cases in which the bicarbonate was administered by mouth, it was given in 10 gm. quantities three times per day. The reaction of each specimen of urine to litmus was tested. The blood specimens were taken each morning before the first dose of bicarbonate. In cases where intravenous administration was employed, the blood sample was taken before each injection.

TABLE V.

EFFECT OF THE ADMINISTRATION OF BICARBONATE UPON THE TITRATABLE ALKALINITY OF THE BLOOD.
ADMINISTRATION BY MOUTH.

Case.	Sodium bicarbonate.	Interval since last administration of bicarbonate.	Behavior of serum toward phenolphthalein.				Reaction of urine to litmus.
			After removal of protein.			1-10 dilution of whole serum in water.	
			In alcoholic solution.	Residue after evaporation.	In aqueous solution.		
H	No color	No color	Pink	Red	Acid
	30 gm.	15 hrs.	Trace color	No color	Red	Red	Acid
	30 gm.	16 hrs.	Red	Red	Red	Red	Acid
	10 gm.	4 hrs.	Alkaline
I	No color	No color	No color	Red	Acid
	30 gm.	15 hrs.	No color	No color	Red	Red	Acid
	30 gm.	16 hrs.	Red	(¹)	Red	Red	Acid
	20 gm.	3 hrs.	Alkaline
J	No color	No color	No color	Pink	Acid
	30 gm.	14 hrs.	No color	No color	Pink	Pink	Acid
	30 gm.	15 hrs.	Red	Red	Red	Red	Acid
	10 gm.	4 hrs.	Alkaline

INTRAVENOUS INJECTION.

A	No color	No color	No color	No color	Acid
	70 gm.	15 hrs.	No color	No color	No color	Pink	Acid
	60 gm.	10 hrs.	No color	No color	Red	Red	Acid
	30 gm.	8 hrs.	Pink	(2)	Red	Red	Acid
D	No color	No color	No color	No color	Acid
	25 gm.	7 min.	No color	No color	Pink	Red
	22 hrs.	Red	(2)	Red	Red	Acid
	25 gm.	16 hrs.	Red	(1)	Red	Red	Acid
Normal	20 gm.	4 hrs.	Red	Red	Red	Red	Amphoteric
	Red	Red	Red	Red	Acid
	5 gm.	3 hrs.	Alkaline

¹ Colorless in 15 minutes. ² Colorless in 5 minutes.

From this table it is seen that the alkali deficit is the important factor in explaining the increased tolerance to bases. It is equally clear, however, that a comparatively small quantity, perhaps 5 or 10 gm., for example, might be held back by

reason of renal retention. Indeed, it would seem very striking if, in cases where there is partial suppression of the ordinary substances, such as dyes, salts, sugars, and water, that the bicarbonate alone should escape partial suppression. A quantity such as 5 gm., however, would be without any clinical significance in comparison with the total amounts which were used.

Some evidence has been collected in regard to the rapidity with which the increase in tolerance to bases returns after the administration of bicarbonate. The period required for the return of the increase in tolerance is so long that only a few cases were available for investigation.

TABLE VI.

DURATION OF THE EFFECT OF THE ADMINISTRATION OF BICARBONATE.

Case.	First test. Tolerance to bicarbonate (grams).	Interval between tests.	Second test.			Tolerance to bicarbonate (grams).
			Behavior of blood serum to phenolphthalein.			
			After removal of protein.			
			In alcoholic solution.	Residue after evaporation.	In aqueous solution.	
H.	70	2 weeks	Red	Red	Red	10
I.....	80	2 weeks	No color	No color	Red	40
J.....	70	2 weeks	Pink	(1)	Red	20
N.....	30	4 days	Red	Red	Red	10—
O.....	20	3 days	Red	Red	Red	10—

¹ Colorless in five minutes.

These data indicate that the effect of the bicarbonate lasts for a relatively long period as compared with diabetic acidosis. Moreover, in the cases in uræmia in which massive injections were used, there was no evidence of rapid neutralization of the injected bicarbonate. These considerations are of special interest from the standpoint of therapy.

Conditions Other than Nephropathies.—Some additional examinations were made in conditions which are of interest in connection with nephritis and uræmia. One of the more important features is the study of the various combinations of cardiac and renal disease. Especial attention has been given to two groups of cases, namely, (1) in which an acute cardiac decompensation has brought about a temporary impairment of renal function; and (2) that group in which renal lesions have brought about a more or less permanent impairment of the cardiac compensation. The various tests for renal function have been employed by different observers to differentiate these two groups; it would seem that those substances would be particularly unsuitable whose excretion is markedly interfered with by an impaired circulation. On the other hand, the more favorable tests would be those which depend upon a long-standing kidney lesion. In this connection it is interesting to note that the excretion of phenolsulphonephthalein is definitely reduced during a break in cardiac compensation, whereas the rest nitrogen of the blood rises but very little, even during long cardiac insufficiency. The changes in the titratable alkalinity in the chronic nephropathies require a long period for their development and, *a priori*, one would not expect such

changes to occur in cases of pure broken compensation. Four patients were tested who were crucial cases for determining the effect of a cardiac break upon the titratable alkalinity of the blood. All of the four cases were in the stage of acute decompensation. This was accompanied by marked cyanosis. Two of these cases subsequently recovered sufficiently to return to their homes. The other two were tested when in complete coma, in extremis, during the last day of life. In these two cases the diagnosis was confirmed at section. In all four of these cases the behavior of the blood serum to phenolphthalein was distinctly normal. It is apparent that this procedure offers a certain amount of information in the differentiation of cardiac and renal cases. However, the exact limits of its value could only be determined by the examination of a large series representing a variety of cases.

Of the other conditions in which there is a dyspnoic coma without diabetes, pernicious anæmia is especially interesting. Seven cases of anæmia were examined. Three of these were secondary to hæmorrhoids. The other four were pernicious in type, two being outspoken cases, while the third (A) was in comparatively good condition. The general results were as follows:

TABLE VII.

CASES OF ANÆMIA.

PERNICIOUS ANÆMIA.

Case.	Red cells per cmm.	Hæmo- globin % normal.	Toler- ance to sodium bicar- bonate, (grams)	Behavior of serum toward phenolphthalein.			1-10 di- lution of whole serum in water.
				After removal of protein.			
				In alcobolic solution.	Residue after evap- oration.	In aqueous solution.	
A	1,800,000	47	10—	Red	Red	Red	Red
B	1,900,000	39	70	No color	No color	Trace color	Red
C	900,000	20	40	No color	No color	Red	Red
D	1,600,000	35	60	No color	No color	Red	Red

SECONDARY ANÆMIA.

E	2,300,000	20	30	No color	No color	Red	Red
F	3,000,000	40	10—	Red	Red	Red	Red
G	2,100,000	35	30	Red	(¹)	Red	Red

¹ Colorless after five minutes.

These cases of anæmia show that, in addition to the impoverishment in cellular elements and of hæmoglobin, the titratable alkalinity is often reduced. Furthermore, in these seven cases the change in titratable alkalinity bore more relation to the grade of anæmia than to the type as determined by the morphological and etiological factors. All of these cases, except the milder pernicious one (A), showed a trace of albumin and a few casts in the urine. It would seem clear, however, that the changes in titratable alkalinity were due to the anæmia, since an even more definite grade of nephropathy gives rise to no changes in the titratable alkalinity of the blood.

On the other hand, the anæmia of the nephritic cases was altogether insufficient to account for the change in titratable

alkalinity. In some of the cases, with the highest tolerance to bicarbonate and with extreme change in titratable alkalinity, the red cell count and hæmoglobin were not reduced more than a fourth of the normal. The results were so entirely independent of the red cell count and hæmoglobin content that it was not considered necessary to record these in the table of nephritic cases.

A few miscellaneous cases were observed in which the titratable alkalinity proved to be of interest. On one occasion a man, 55 years old, was admitted to the hospital in coma with a history of anuria for 15 hours and a record of chronic nephropathy extending over 35 years. The respirations were deep and regular, but were not increased in frequency, and expiration was not prolonged. The mucous membranes were normal in color. Ten cubic centimeters of urine were obtained by catheter. An abundance of albumin and a variety of casts were present. No additional information could be obtained on further examination. The diagnosis lay between uræmia and cerebral hæmorrhage. An examination of the blood serum showed a normal condition as regards rest nitrogen and titratable alkalinity. The secretion of urine commenced in a few hours, the albumin and casts disappearing almost completely within a few days. Later a history was obtained of partial paralysis of short duration in the left arm, coming on about two weeks before admission to the hospital. The subsequent record of this case confirmed the diagnosis of cerebral hæmorrhage.

In a second instance, the patient was a man of 45, who had some knowledge of medicine. A definite nephritis of moderate grade was known to have existed for several years. This patient suddenly developed attacks of dyspnœa characterized by comparatively rapid respiration, without cyanosis, and with subjective symptoms of air hunger. The absence of any physical changes in the chest, the irregularity of these attacks and the absence of any relation to physical exertion, indicated that they were neurotic in origin. Nevertheless, the possibility of an air hunger due to renal lesions could not be excluded clinically without further observation. The examination of the blood serum at this time showed only a slight decrease in titratable alkalinity. The residue after evaporation of the alcoholic extract did not lose its red color until after heating for 15 minutes on a steam bath. This would indicate a diminution in titratable alkalinity which would be far too slight to give rise to subjective symptoms.

Brandenburg¹³ divides the alkaline content of the blood into two fractions. The first is the diffusible or mineral alkali. This is small in amount and consists largely of the carbonates of the blood. The second and larger fraction consists in that which is bound to the protein. Brandenburg considers that the second fraction is subject to variation and that the diffusible carbonates are relatively constant. The behavior of the alcoholic filtrates from serum point toward the reverse conclusion, for it is largely the carbonates which are removed by the alcohol. The discrepancy, however, may be only appar-

ent, for the statements of Brandenburg may apply more particularly to the very early changes in the titratable alkalinity of the blood.

Quantitative Determination of Changes in Titratable Alkalinity.—Throughout this paper only the more important qualitative changes have been studied. The principal objection to quantitative work on titratable alkalinity lies in the inaccuracy of all procedures due, in part, to the small amount of the substances to be measured, and also to the extremely poor end-points obtained with the indicators which are alkaline to normal serum. However, the removal of protein obviates one of the difficulties with the end-point afforded by the indicator. It would seem that the sharp reaction obtained with phenolphthalein after removal of the protein should be susceptible of expression in some quantitative form even though minute quantities of alkali are handled. Several methods suggest themselves for clinical purposes, such as direct titration, colorimetric measurement, determination of the dilution at which the color disappears in the heated aqueous dilution, or the determination of the minimal amount of normal serum which will suffice to give a color reaction in the alcoholic filtrate.

A number of titrations were carried out according to the following technique: 1 cc. of serum was diluted to 25 cc. with absolute alcohol and the mixture filtered after thorough shaking. Twenty cubic centimeters of the filtrate was evaporated to dryness on a water bath and taken up in 10 cc. of water. Five cubic centimeters of N/125 sulphuric acid were added to the residue in order to titrate subsequently for the appearance rather than the disappearance of color. The titration was carried out at boiling temperature with N/125 sodium hydroxide and phenolphthalein. The number of cubic centimeters of N/125 sulphuric acid which were neutralized by the alcoholic residue, represent the titratable alkalinity of the original serum expressed in per cent of a normal solution, or rather that fraction of the titratable alkalinity which is removed in the alcoholic filtrate. Normal serum, under these conditions, gave values varying from 0.8 to 1%, and the pathologic sera, which gave a qualitative reaction for alkali, gave results varying from normal to a trace. However, the work of keeping the dilute standard solutions accurately balanced and the comparatively slight amount of information afforded did not seem commensurate with the time involved. The test simply in its qualitative form is sufficiently delicate to detect readily a grade of acidosis which has any clinical significance. For clinical purposes, however, it would seem quite feasible to adapt some simple colorimetric standard of measurement, or perhaps reduce the amount of serum employed to the minimum which will give a satisfactory color reaction in known dilution in alcohol. Another modification which readily suggests itself is the use of the whole blood without waiting for the separation of the serum. In a few preliminary tests an alcoholic filtrate did not give an alkaline reaction with phenolphthalein when whole blood was used instead of serum alone. This might have been due partly to the hæmoglobin and also, perhaps, to the large masses of precipitate formed by the whole blood which increased the difficulty of extraction.

¹³ Emerson: Clinical Diagnosis, 4th ed., Phila., 1913, p. 569.

Physico-chemical Reaction of the Blood.—The work throughout this paper has been confined to the titratable alkalinity of the blood. The study of the physico-chemical reaction of the blood in health and disease did not seem appropriate under the present conditions for two reasons: In the first place, although investigators are not yet fully agreed as to the accuracy of either the colorimetric or the electric measurements of physico-chemical reaction in the presence of protein, yet the consensus of opinion is that the reaction of the blood undergoes comparatively little change even during an acidosis. The most recent work from Sørensen's¹⁴ laboratory with improved methods for electric measurement indicates that the compensatory processes of the body are sufficiently effective to maintain a comparatively normal physico-chemical reaction of the blood, even during an acidosis. In addition to the uncertainty which still surrounds the application of the physico-chemical methods in the study of the reaction of the blood, it is evident that the observations on the titratable alkalinity offer a much simpler procedure for clinical purposes. Moreover, the weight of evidence tends to show that it is the titratable alkalinity rather than the physico-chemical reaction which is subject to variation and which consequently is of importance from a clinical standpoint. This view was suggested by Folin¹⁵ at an early date and at a time when the first application of physico-chemical methods to the blood were frequently interpreted as indicating that the older titration procedures were erroneous and should be abandoned.

SUMMARY.

1. Changes in the titratable alkalinity of the blood occur which give rise to distinct qualitative differences in the reaction of normal and pathologic sera to phenolphthalein. Conditions are readily obtained under which the blood serum,

¹⁴ Sørensen: Personal communication.

¹⁵ Folin: Trans. Ass. Am. Phys., 1907, XLIX, 128.

during an acidosis, is neutral or acid, whereas under the same conditions all normal sera are strongly alkaline.

2. The less severe grades of diminished alkalinity can be detected in a qualitative way from the behavior of sera before and after the removal of protein and by the selection of a solvent, such as alcohol, in which the ionization and hydrolysis of carbonates are diminished. The effect of protein and of the solvent upon the reaction permit a variety of combinations of these factors for detecting varying grades of diminished alkalinity.

3. Definite changes in the titratable alkalinity occur in experimental and spontaneous acidosis, in certain nephropathies, and in some anæmias. The method also affords information of value in the differentiation of certain obscure comas.

4. Cases of diabetes occur in which the excretion of ammonia and of acetone and related bodies is normal, but the titratable alkalinity is decreased and the tolerance to bases is increased. This affords proof of a definite impoverishment in bases in these cases.

5. Changes in the titratable alkalinity are accompanied by corresponding changes in the tolerance of the body to fixed bases.

6. The titratable alkalinity is of important biological significance, while the available evidence indicates that the physico-chemical reaction of the blood is maintained at a fairly constant value, even in outspoken grades of acidosis.

7. The parallelism between the diminution in titratable alkalinity and the increase in tolerance to fixed bases in diabetes and in the nephropathies affords crucial evidence that this increase in tolerance is due practically altogether to a deficit of the body in alkalies or alkali-yielding substances. The questions as to whether such a condition constitutes an acidosis will be discussed in a subsequent paper.

It is a pleasure to thank Dr. Lewellys F. Barker for an interest in this work which has been very helpful.

SOME ERRORS IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS.*

By LAWRASON BROWN, M. D., Saranac Lake, N. Y.

It is a curious psychological fact that the mistakes of another practitioner, when narrated with a more or less complete medical history, rarely impress the listeners in any way other than avoidable. I was well aware of this when I imprudently suggested to Dr. Hamman that I would speak to you to-night of some of my errors in diagnosis and mention a few made by other men. The only medical man who has made no mistakes is the second or third year medical student just entering upon his clinical work. Some of these mistakes of mine would never have been made had the patient and myself been able to enjoy the privilege and co-operation of such a hospital staff as you have here. The limitations of private practice must be experienced to be realized. The physician must in many cases depend entirely upon his own powers of observation

for such assistance as he can command in a small town among poor patients.

A hint from a wide-awake colleague, a member of the house staff or from a keen nurse, may recall to mind another case that makes the diagnosis clear. I shall present to you a number of brief histories of patients and endeavor to help you to see how I fell into error. I am fully aware that many men, keener of observation than I, would have had more data upon which to base judgment and so probably have avoided these pitfalls.

I have no doubt that I was taught in my classes in physical diagnosis that muscle sounds could in rather thin muscular subjects simulate râles, but when I told a medical student a few months after my graduation that his disease extended over the posterior of both lungs I had forgotten this fact, and later learned that he had a just discoverable apical lesion which has remained healed for thirteen years. I had never grasped the

* Read at a meeting of The Laennec, a Society for the Study of Tuberculosis, The Johns Hopkins Hospital, January 26, 1914.

fact that shoulder friction could lead me to believe that a patient had pleurisy in the interscapular region, but it did. Swallowing can produce sounds in the upper chest so closely resembling râles that I had to learn that fact also. It took me many years to learn that disease could exist for a time without physical signs and that not infrequently as the patient improved the physical signs became much more extensive.

I still make yearly some mistakes in regard to the presence or absence of a pleuritic effusion. The signs seem to me in some cases, when limited in area, to be very difficult of interpretation, and the needle is of course the only test, and that even is not infallible. More difficult still is it to determine whether or not any fluid remains in the chest after repeated aspirations. I shall narrate the history of a case a little later where I found it most difficult to decide. The heart may not be displaced and the side not increased in size.

1. Some ten or twelve years ago I had referred to me by one of the physicians in the Johns Hopkins Dispensary, a patient who had been acutely ill with what seemed like the grip. She had, as I now recall it, no temperature but some cough and expectoration and râles all over the posterior of one lung and the upper half of the opposite. She applied to me for admission to the Adirondack Cottage Sanitarium and I refused her. One month later when I re-examined her, to my astonishment I found her lungs normal. An acute process was clearing up irregularly on the two sides.

2. One hot afternoon some ten years ago I was called to a little back room to see a poor woman, thirty-five or forty years of age, with high fever, very pale and weak. She was said to have tuberculosis and I immediately suspected an acute miliary tuberculosis. The lungs showed no definite signs on repeated examinations, only a very few glands were slightly enlarged and I finally obtained her admission into the Reception Hospital, where after concurring at first in the diagnosis of pulmonary tuberculosis, Dr. Baldwin made a diagnosis of Hodgkin's disease, later confirmed by the microscopic examination of a gland excised after death.

3. About seven years ago (1907) a young man, aged twenty, was under treatment by me for pulmonary tuberculosis off and on for two years. Tubercle bacilli were present in the sputum. He then returned home and to a fast life and contracted gonorrhœa and lues. One year later he had some swollen cervical glands removed which were said to be tuberculous. A year after this, two years after I had seen him, he sent for me again, saying he had had fever of 104° F. for three days. On examination, the old scar in the neck was very evident and about it were a few small glands. The right upper and middle lobes were infiltrated and showed a slight advancement of the lesion. Otherwise the physical examination was negative except Babinsky's sign was present and the reflexes were possibly a trifle increased. Four days later the patient exhibited nervousness and twitching, more on the left side and at night (so the nurse said). There was no retraction of the head and no Kernig's sign. At this time a consultant diagnosed meningitis of which I was not sure but felt that he must have obtained data which I had overlooked. The temperature remained at 104° F. for four more days (eleven in all) and then fell by crisis to normal. The sputum was negative for tubercle bacilli; and except for an occasional trace of albumen and one finely granular cast the urine was negative. The blood contained 77% of hæmoglobin, 3600 leucocytes and 5,076,000 erythrocytes. A differential count of 250 cells showed 62.8% of polymorphonuclear neutrophils, small mononuclears 20%, large mononuclears 13%, transitionals 3.6%. On the 7th day of the fever, a count of 200 cells showed only 39% of polymorphonuclears, 18% of large mononuclears and transitionals and 43% of small mononuclears. Three weeks later a similar blood picture was found. The complement

deviation test for tuberculosis was negative once and for syphilis twice. A spinal puncture was not made. A Widal test and a blood culture were negative. After eight days of apyrexia, the temperature rose gradually to 105° F., the twitching returned and it was again thought that the patient would die, but after sixteen days of pyrexia the temperature fell once more to subnormal and the symptoms largely disappeared. After fourteen days of apyrexia a third attack with a temperature of 105° F. lasted for twenty-two days, during which he was seen by Dr. S. W. Lambert who made a diagnosis of Hodgkin's disease. The spleen at this time was enlarged, the liver dulness somewhat increased and a few glands were palpable in the axilla. He died a few weeks later.

I had sufficient data to diagnose Hodgkin's disease, and why the first consultant and I thought of and excluded nearly everything else I cannot say and offer no excuse.

4. In August, 1911, a clergyman, aged about thirty-five years, came to me saying he had begun to feel badly four months previously. One sister had had pulmonary tuberculosis and recovered. Three weeks previously he had had night-sweats, shortness of breath, fever and felt weak. After five or six weeks in the Catskills he came to Saranac Lake. He was somewhat anæmic, had lost weight and his general condition was poor. The pulmonary examination showed signs of fluid (previously diagnosed) to the level of the third rib and third vertebral spine. His sputum contained no tubercle bacilli and the urine a trace of albumen and a few hyaline casts. He had continuous fever ranging about 100° to 101° F. He was aspirated repeatedly and the fluid never showed any tubercle bacilli either by animal inoculation or by staining. However I thought the patient had a tuberculous pleurisy and treated him accordingly. Between two and three months after his arrival, a slight swelling appeared in the third right intercostal space. It grew larger and larger, redder and softer. I diagnosed a cold abscess on a rib and my assistant incised the swelling but could get no pus. A little later another appeared on the opposite side of the sternum. The glands in both axillæ and above and below the clavicle then enlarged slightly. The mental condition of the patient was very peculiar. He had constant but always changing delusions of persecution which finally largely cleared up. The mass over the sternum became larger and more irregular. A blood count showed a leucocytosis of 21,000 and in a differential count the polymorphonuclear neutrophils were 92%, lymphocytes 7%, large mononuclears 0.5%, eosinophiles 0.5%. A bit of tissue removed before death from the mass showed the characteristic picture of Hodgkin's disease, which was confirmed by a second specimen taken after death.

I thought this patient had a tuberculous effusion and later, as I said, a cold abscess. The pathologist in this case helped make the diagnosis, but like some few pathologists he left himself a loophole large enough for escape.

When the superficial glands are enlarged the differentiation of Hodgkin's disease from tuberculosis is at times difficult, but in two cases that I have seen the only difficulty lay in thinking of Hodgkin's disease, which by the way is not always as easy in general practice as some of the third and fourth year students imagine. One of these cases was so far advanced that she died in one week after reaching the Adirondacks. The other was operated on for so-called tuberculous glands of the neck, and the tonsil on the same side removed four years ago. The removed glands were not examined in this case or the other, which was also operated on for tuberculous adenitis, nor was Hodgkin's disease even suspected by a number of medical men who had seen the patients.

Here, then, are five cases of Hodgkin's disease, all of which

were sent to the Adirondacks for tuberculosis. In two the superficial glands and spleen were enlarged and the diagnosis should have been made and the patients kept at home. In the other three the superficial glands did not enlarge at all or only very late in the disease. An indefinite onset followed by pleuritic effusion and fever is likely to lead anyone astray. When enlarged glands occur in a tuberculous patient and do not recur after removal or remain very small, it is not easy to diagnose lymphadenoma. I have no doubt a number of cases have escaped me, but to-day I am on the outlook for such cases and that, I believe, is a large factor in their correct diagnosis.

5. In the winter of 1912, a school teacher, fifty years old, from the Middle West was sent to me suffering from pleurisy with effusion. I immediately took it for granted that a diagnosis of tuberculous pleurisy had been made, as I believe it had. He complained of great pain over the left anterior costal margin and a fast pulse. One brother died of tuberculous laryngitis. He denied lues and tripper, but had pneumonia when a child. Fourteen months before he saw me he had been treated on account of the pain for indigestion. Not improving he went to Battle Creek where fifty ounces of a clear fluid, of low specific gravity, containing no pus, were withdrawn. He returned home and tried to but could not continue work. One month previous he had nearly lost the use of his left side, and since then the left palpebral orifice has been smaller than the right. Hoarseness then occurred and loss of weight and strength. His appetite was poor and bowels very constipated. He had slight expectoration. A radiograph was said to show a thickened pleura and some intrapulmonary disease on the left with scars of an old tuberculosis on the right. He stated that he had had little or no temperature but that his pulse was fast and he was slightly short of breath and slightly aphasic. His chief complaint was pain at the left anterior costal margin, so severe that he could sleep only when he lay on his back and then only when he took analgesics. The left side was depressed, moved less, showed loss of vocal fremitus and almost flatness over most of the side. The breathing was distant, the vocal resonance decreased and there were a few scattered râles. There were possibly a few fine râles in the outer third interspace on the right. The heart was not misplaced. The sputum contained some tubercle bacilli ten days after arrival and the urine was normal. Three weeks later his voice became more husky and weak, due to a paralysis of the left recurrent laryngeal nerve. Two months later, after a dry tap in front, 400 cc. of a reddish brown fluid with many polymorphonuclear and few mononuclear cells were aspirated posteriorly. A differential blood count was normal and when five months after arrival the liver was found enlarged, a negative Wassermann was obtained. There were no glands except one the size of a hazel nut in the left axilla which decreased in size. The patient returned home and as my diagnosis of malignant tumor of the lung and pleura was not acquiesced in, a laparotomy was done and revealed a liver studded with carcinomatous nodules. He died a few days after the operation. As I said at first I thought the patient had tuberculous pleurisy but as the other signs developed the diagnosis seemed untenable. He may have had pulmonary tuberculosis also as tubercle bacilli were found in the sputum at the Adirondack Cottage Sanitarium or some mistake may have occurred as at no other time were they ever demonstrated.

This case and the case of the clergyman with Hodgkin's disease show how easy it is to be misled by the presence of fluid.

6. Two years ago a woman, aged 50, the mother of two children, was referred to me for treatment. One brother died of tumor of the lung, otherwise the family history was negative. Thirty years previously she had had for about three years, attacks of

bronchitis lasting about two or three months each. Her health continued good until one and a half years ago when the left breast was removed and the axilla cleaned out for a typical mammary carcinoma. She was then well until about eight weeks previously she had a slight hæmoptysis and had ever since raised blood streaked sputum in which tubercle bacilli were found. A few physical signs were discovered at the right apex and the lymphatic glands in the right cervical region were found enlarged. Pleurisy in the right infraaxillary region developed three weeks previously and the temperature rose to 100.5° F. and 101° F. Following this the temperature varied from normal in the morning to 100° F. at night. Three weeks previously her right knee began to pain her and continued to do so. The finding of tubercle bacilli convinced the hospital authorities that she had pulmonary tuberculosis and her attending physicians were considerably chagrined as they had not discovered them on several examinations. When she came under my observation June 29, 1912, she was in bed expectorating blood and had a slight elevation of temperature. I kept her in bed and only at the end of a week did I examine her lungs, for the blood spitting continued. A few scattered rhonchi were heard over the upper lobe of the right lung. The examination of the sputum and urine were negative and I thought the patient was probably tuberculous with possibly carcinomatous or tuberculous glands in the neck on the side opposite the former tumor. Two weeks (July 12) after arrival the breathing was noted as being slightly distant and broncho-vesicular above the left clavicle but no dulness could be made out. Four days later (July 16) the breathing on the right was puerile, on the left distant over the front but of good quality. On the left back there was dulness, more pronounced below. The breathing was less marked than on the right and after coughing a few sonorous râles were heard. The heart sounds were more widely transmitted than normally. The cough had now become spasmodic and suggested intrathoracic pressure and she had difficulty in breathing. The next day there was dulness over the greater part of the left lung, with flatness below, whispering bronchophony was audible to the fifth rib and eighth vertebral spine, but vocal fremitus was lessened. The breathing was distant. Three days later a dry tap was obtained. On July 28, the knee was put up in crinoline. The next day double vision occurred and several days later a marked internal strabismus of the left eye occurred. Later vomiting occurred frequently. From this time on the symptoms gradually increased until weakness lessened them. The only point of interest which developed before her death on September 3 was that she had attacks of premature cardiac contraction, apparently ventricular in origin. Her headache would increase and the pulse drop from 132 to 60 and in one-half hour rise to 120. On one occasion it dropped to 38. I diagnosed secondary carcinoma of the lungs, cervical glands, brain and knee, but the autopsy performed by Dr. Krause revealed a hypernephroma on the right side with metastases to the left lung, two or three to the right lung, to the liver, left kidney, right knee and a few nodules in the mesentery and retroperitoneal tissues. The brain and neck were not examined. A few weeks ago, the sections from the mammary carcinoma were examined by Dr. W. G. McCallum, who pronounced the tumor a typical carcinoma.

7. A youth, aged 19, from New Jersey, applied for admission to the Adirondack Cottage Sanitarium last summer. His family history and his previous history were unimportant except that he lived under poor hygienic conditions and was closely associated with a boy friend who was tuberculous. About six or seven weeks before admission (March, 1913) he began to lose appetite, weight and strength, had a slight cough and suffered from languor. One and a half months later he had night-sweats, fever and sputum. On arrival in Saranac Lake one and a half months before admission he had temperature of 101° F., night-sweats and physical signs interpreted as due to enlarged bronchial glands. After admission he grew worse and was transferred to the infirmary where his

temperature ranged from 97° to 102° F., but many days never fell to normal; his pulse varied from 100 to 120, his respirations from 16 to 28. On October 12, seven months after onset, his leucocytes were 38,000 and the polymorphonuclears 92%. A radiograph showed a shadow in the mediastinum, about five inches in breadth, some diffuse consolidation in the lower part of the right lung and some consolidation about the hilus of the left lung. The note on the right was markedly dull below the sixth vertebral spine, the breathing somewhat exaggerated over the whole front, the vocal resonance normal, a few fine râles were heard at the inner end of the fourth interspace and moderately coarse râles below the fourth vertebral spine. On the left the note was hyperresonant over the lower front, the breathing slightly distant over the front. A few scattered moderately coarse râles after coughing were heard over the front and fine râles to the third vertebral spine. The following day a fluoroscopic examination confirmed the radiograph and showed the posterior mediastinum to be free. A diagnosis of mediastinal abscess was made and the introduction of a needle was considered. The second day following there was flatness from the right of the sternum extending over most of the left front, the vocal resonance was increased and the breathing markedly weakened. The patient expectorated some dark clots of blood. The urine examination was negative and the purulent sputum never showed any tubercle bacilli. The radiograph showed that the whole mass had shifted slightly to the left. At this time a mediastinal abscess was diagnosed and the patient referred to a surgeon who diagnosed malignant growth. After several days of observation a thoracotomy revealed sarcoma of the mediastinum and left lung which was confirmed by histologic examination of a piece of excised tissue. I should have made this diagnosis but the sudden change in note led me astray as well as the sharply defined right border of the X-Ray shadow and the positive opinions of some other medical men.

In these three cases of malignant tumor of the lung and pleura, it is curious that in two tubercle bacilli were found once but never again in the sputum. One patient might have had a tuberculous focus in the lung, but in the other it was excluded at autopsy. The pleuritic effusion, the reported presence of tubercle bacilli in the sputum and the fever would easily mislead anyone in the first case, while only the presence of tubercle bacilli in the sputum in the second case led one to think of anything else than a pulmonary metastasis. In fact her attending physician suspected this, but the hospital authorities were so positive of the presence of tubercle bacilli that they yielded. When a patient comes from well recognized authorities with a diagnosis made by finding tubercle bacilli in the sputum, it is well to go very cautiously before stating that their laboratory has made a mistake. The same thing, however, probably occurred with us. When the physical signs of pulmonary tuberculosis are anomalous it is wise to check up the diagnosis made from the sputum. I ought, no doubt, to have diagnosed hypernephroma, but the patient was very fat and had I felt the tumor I would, I am sure, still have called it a metastasis, for I did not then know that hypernephromata are not rare in patients who have had carcinoma.

8. A lawyer, aged 54, complaining of pulmonary tuberculosis, consulted me some seven years ago. Several members of his immediate family had suffered from and died on account of circulatory disorders. The personal history was unimportant except that he had had a slight cough for seven years, due, he said, to tobacco. While he had been exposed, no history of lues was obtained. Three of four years before I saw him he began to lose weight and strength, but recovered and was well until several months pre-

vious, during which time he had had temperature which for a few weeks ranged from 99° to 103° F. With this acute attack his cough and expectoration had increased and his physician had found tubercle bacilli in his sputum. On examination his general condition was poor, his color not good, his radial arteries thickened, pulse 100, and his second pulmonic accentuated; temperature 97° F. The pulmonary examination showed on the right: slight dullness to the third vertebral spine with good vesicular murmur, fine râles to the clavicle and third vertebral spine after coughing; on the left the side was much contracted, the vocal fremitus increased and some dullness over the entire back; the vocal resonance was increased, broncho-vesicular breathing was present to the clavicle, coarse râles were heard in the outer fourth and fifth interspace and from the sixth vertebral spine to the base. A few fine râles were present at the base anteriorly. On these data I made a diagnosis of pulmonary tuberculosis. Three examinations of the sputum were negative for tubercle bacilli and the urine was normal. His pulmonary condition improved rapidly. His temperature was normal, pulse from 100 to 108. Two months after arrival he spat blood two or three times, had slight elevation of temperature and pain in the right lower chest. Two weeks later phlebitis occurred. One month later when his lungs were nearly normal, he had a sharp pain at the base of his neck, fell off his chair and became unconscious. On regaining consciousness he vomited such large quantities of fluid that a physician made a diagnosis of acute distension of the stomach. Later in the day a few signs of intrathoracic pressure developed and that night he died suddenly. Autopsy revealed a dissecting aneurysm of the arch which had followed the pulmonary artery well into the lungs. The lungs were otherwise normal. He had had fever, hæmoptysis, phlebitis, cough, expectoration and so-called tubercle bacilli in his sputum which his physician stoutly maintains to this day were real tubercle bacilli.

I do not see how I could have avoided this mistake.

9. Last month the name of an actress, married, aged 30, was placed upon the waiting list for the Adirondack Cottage Sanitarium by one of our examining physicians. One uncle had died from pulmonary tuberculosis. Twenty years previously she had had inflammatory rheumatism and her heart was said to have been affected. However, she did as other children and when she went on the stage as a chorus girl she danced hard and sang. Last spring (1913) she went on a tour to the Pacific coast and on the return trip became ill with cough, expectoration and fever and both in Saskatoon and later in Winnipeg was told she had pulmonary tuberculosis. After a three weeks cure in Liberty she joined a company in New York and rehearsed hard. Becoming hoarse she saw a throat specialist, who referred her to our examining physician, both of them concurring in the diagnosis of pulmonary tuberculosis. Early in December she reported at the Examining Office in Saranac Lake and was advised to go to bed on account of her fever. The physical signs at that time were very slight on the right side. She sent for me a little later on account of the fever and rheumatism in the right knee. I heard nothing in her lungs but regret to state that as the room was very cold and both the patient and myself very uncomfortable, the examination was more cursory than usual. There was some enlargement of the heart and a loud systolic murmur, transmitted to the axilla and back, with the maximum intensity over the point of maximum impulse in the fifth interspace in the mid clavicular line. She had no swelling of the ankles. She had a severe cough for which I gave her a good "tuberculosis" cough mixture, but the temperature persisted until one night I was sent for as she could not "talk straight." She knew what she wanted to say but could not say it. Her right arm became paralyzed and the knee kick was absent on the right and marked on the left side. The pupils were constantly small and sluggish. The next day at 9 p. m. she gave a cry and moaned. Kernig's sign was present in the left leg for a

time. Babinsky's sign was present in both sides. The blood pressure was systolic 115 mm., diastolic 70 mm. A spinal puncture revealed a bloody fluid not under much pressure. The second day after the onset she moved her right arm but developed stertorous breathing and died that night, having been unconscious most of the day. Autopsy revealed a hæmorrhage into the left lateral ventricle and some over the convolutions about the fissure of Rolando. Her heart showed a chronic mitral lesion and a beautiful acute endocarditis. In the right lower lobe was a firm, dry patch about 5 x 5 cm. and on section like hepatization, but containing air, while the rest of the lung was œdematous. There was no tubercle. This patch could have given some signs and misled, I believe, several physicians.

What had happened was, I suppose, as follows: An embolus had lodged in a small branch of the middle cerebral artery leading to a silent area of the brain. This area had softened and with absorption of the embolus or after the formation of an aneurysm, rupture had slowly occurred and the blood oozed out. I do not see why an apical infarct might not lead to mistakes in diagnosis. I heard of a patient who was admitted to a large New York hospital, as she had heart disease and the pulmonary tuberculosis was too advanced in the apex or apices for treatment in the Adirondack Cottage Sanitarium. As her heart condition improved her lungs finally cleared up completely.

10. In the summer of 1911, a woman, married, aged 29, from Pennsylvania, sent for me and complained chiefly of pain in the back. The family history was negative and the previous history unimportant. She lived under good hygienic conditions and had never been about cattle or stables. The present illness began about ten months previously with an indefinite attack which was attributed to a floating kidney. Two and a half months later (March, 1910) she went to Augusta, Ga., for six weeks. After her return she began to cough, but only slightly at first. The following fall (November, 1910), she was so weak she went to bed for a five months rest cure. This followed by a six weeks visit to Cambridge Springs resulted in a gain in strength and weight, but with the hot weather of June the cough increased and she felt worse. In July, eighteen months after the onset, she noticed a painful and tender swelling over the right lower thorax posteriorly. Disease of the spine or rib was diagnosed, but no fluid was obtained on puncture. In August when I saw her she complained chiefly of pain in her back. She was very thin, weak, nervous and with marked pallor. The heart was apparently normal and not displaced. The right side was much contracted, moved less, with much increased vocal fremitus to the third rib. There was some dulness over the back, most pronounced below the seventh vertebral spine and bronchial breathing to the clavicle and third vertebral spine and opposite the fifth and sixth vertebral spines with increased vocal resonance. Moderately coarse râles were heard over the side on coughing. On the left the vocal resonance was somewhat increased in the axilla. There was marked rigidity of the spine, tenderness over the ninth and tenth dorsal vertebræ and brawny swelling along the spine from the eighth to the twelfth dorsal vertebræ. I informed the husband that she had extensive disease of the lungs, probably tuberculous, and also in all probability disease of the ribs or vertebræ. The temperature ranged from 99° to 100.5° F. and the swelling slowly increased in size and softened in the center. About this time marked rigidity developed in the right abdominal muscles. The urine was normal. The leucocyte count at this time was 15,000, the differential about normal. I had a surgeon see her and he though she had empyæma, probably tuberculous in origin, and advised aspiration, saying there was nothing wrong in the abdomen. A few drops of bloody, glairy fluid were obtained on aspiration which on examination contained no tubercle bacilli, but some

Gram positive cocci and rods with some Gram negative ovals. About this time the patient acknowledged that she had a little sputum which was negative for tubercle bacilli. In September, two months after her arrival in Saranac Lake, the swelling was incised and under the skin a curious, rather friable, stringy, bloody tissue was found which bled freely. The abscess contained bloody, glairy, rather thick, tenacious pus, full of minute, sulphur yellow particles, slightly less than one millimeter in diameter. They proved to be actinomycotic granules, and the organism was cultivated later and found in the sputum. She died May 12, 1912. I should have suspected actinomycosis sooner but this was only the second case which I have ever seen. The first was a patient in the Johns Hopkins Dispensary.

11. In the summer of 1912 (August 24), a married woman, aged 41, wife of a professional man, came to my office saying her lungs were diseased. The family and previous history were unimportant. The present illness dated from November, 1911, nine months previously when she had a "cold" and was in bed with cough and expectoration for two weeks. She said she had had night-sweats, fever, some hoarseness, pain on the front of the chest, shortness of breath, loss of weight and strength, and cough and expectoration. She had spat blood-streaked sputum, but thought it might be due to whooping cough, which she might have contracted from her adopted son. The temperature was 99.6° F., pulse 128, respirations 20, her general condition was poor and she had slight pallor. She said no tubercle bacilli had been found in her sputum. The pulmonary examination showed rhonchi to the third rib on each side and to the fifth vertebral spine on the right, as well as fine râles to third rib on the right. I promptly made a diagnosis of pulmonary tuberculosis and put the patient to bed. During the next month she remained in bed, had a temperature ranging from normal to 101° F., pulse 88 to 116, usually 100, and respirations 20 to 26. Her cough was severe and the sputum at times was slightly blood tinged but contained no tubercle bacilli. The lungs cleared up and only an occasional fleeting rhonchus was heard. She was very erratic. Her brother came to see her five weeks after her arrival and told me of a marital infection with lues. Two Wassermann's were positive and a couple of intravenous injections of salvarsan brought the temperature to normal and the patient returned home and has been well since.

12. Several years ago a married woman, 27 years old, the mother of four healthy children, consulted me, complaining that she had high fever (103-105° F.) much of the time for three years. Her family and previous history were negative. Three years previously, while nursing a child with typhoid fever, she began to have fever and was treated for typhoid at first and later for malaria. As the fever persisted she was sent to Asheville and then kept in bed for months. The temperature finally reached 99° F., but on return home it again rose and her physician sent her to me. She had lost strength and had night-sweats, but her weight was normal, her bowels regular. The temperature in the office was 100.8° F., pulse 116 and respirations 24. The general condition was good and there was only slight anæmia. The heart was not enlarged, the abdomen negative, the urine normal and there was no sputum. The lungs were apparently normal and a gynecological examination was negative (W. Griffith). Both she and her husband denied all symptoms of lues. I referred her to Dr. Fitcher who told me the Wassermann reaction was positive, but the temperature did not become absolutely normal for a time. She, however, made a complete recovery.

13. About ten years ago, a farmer, married, aged 47, from New York State, consulted me as he had had repeated hæmoptyses. One aunt died from tuberculosis. He had had cough and expectoration for thirty years, dry pleurisy as a boy and pneumonia many times. His present illness he dated two years previously, when he had his first hæmoptysis. He had had slight hoarseness, much

cough and expectoration, some shortness of breath and some loss of strength. He was slightly pale, had a temperature of 99.3° F., pulse 96 and had lost nine pounds in weight. The physical examination revealed only a few moderately coarse râles below the seventh vertebral spine on the right. The urine showed few hyaline and granular casts and the sputum was repeatedly and always negative for tubercle bacilli. Pneumococci and influenza bacillus were looked for but the results were inconclusive. The patient finally decided to remain permanently in Saranac Lake. I saw him off and on for blood spitting and he was fairly well, still with cough and expectoration, until the fall of 1910 when he had cholecystitis and during convalescence hæmorrhage into his internal capsule on the right, which caused in a few days his death. The autopsy showed besides these complications, a chronic bronchiectasis of the right lung.

This case shows the fallacy of always accepting hæmoptysis as due to pulmonary tuberculosis, but only his history at first could have excluded pulmonary tuberculosis and that was only negative evidence.

14. In the summer of 1910, a broker from New York, aged 50, consulted me as he had had fever and felt badly. His family and personal history were unimportant. Three months previous to his arrival in Saranac Lake he had a rather atypical attack which resembled pneumonia and had not been well since. Malaise had been pronounced and cough, expectoration, fever, night-sweats, shortness of breath and pain in his right side were marked. Once or twice he felt as if his right lung was choked up. He went from place to place and early in August came to see me. His temperature was 100.8° F., pulse 120, general condition poor. On examination, dulness was marked over his upper lobe with bronchial breathing and vocal resonance markedly increased. Fine râles were heard over the back and a few over the lower back on the left. The relative heart dulness apparently extended to the right of the sternum. There was pain radiating to the right shoulder when pressure was made on the abdomen. The sputum was purulent, at times tinged with blood but always negative for tubercle bacilli. The urine was normal. I felt uncertain about the diagnosis and had a colleague see him with me. He made a diagnosis of pulmonary tuberculosis. During the month he was under my observation the physical signs remained normal on the left side, but on the right, the dulness increased slightly, the breathing over the lower two-thirds of the chest was less pronounced and moderately coarse and fine râles were present over the side. Pneumococci were found in the sputum and I wanted to give him a vaccine which he refused to take. He then went to Montreal where a little later a radiograph showed a cavity. The physical signs increased and hyperesthesia developed below the third rib and above the third vertebral spine. Operation was considered, but not done until the pulmonary abscess jointed about the fourth rib under the scapula. A pure culture of pneumococcus was obtained. The patient sank gradually and died.

I feel I should have made the proper diagnosis in this case, but many points I have brought out were not emphasized in my mind until later. I was, however, always skeptical about the condition being tuberculous.

15. Two and a half years ago a trained nurse, aged about 25, was sent to me from New York. She complained of elevated temperature and at times slight cough. She had had temperature of 100° to 101° F. for many months and had consulted the best men in Philadelphia and New York. In the latter city she fell into the hands of a surgeon who opened the abdomen from the ensiform cartilage to the pubes but found nothing. Her radiographs were negative and she was referred to me as it was thought possible she might have a tuberculous pulmonary focus. The lungs were always normal and nothing abnormal of any moment was found anywhere. The urine, the blood (including a Wassermann) and the feces were apparently negative. The patient was kept in bed and then as it did not affect the temperature she was allowed to get up. In short, the temperature persisted for about sixteen months and finally disappeared. So the diagnosis of a localized miliary tuberculosis could not be verified. She is, so far as I know, well to-day.

A physician who lives in a health resort for pulmonary tuberculosis and limits his practice largely to that disease, does not have the same opportunity for making mistakes that a man in general practice has. On the other hand he can easily fall into the error of thinking that every patient has without question pulmonary tuberculosis. Fourteen years ago we had many patients reach us in the final stages of the disease. To-day the problem is changing and we are kept busy constantly endeavoring to prove that some of our patients have pulmonary tuberculosis. We are more likely to call other disease pulmonary tuberculosis than the opposite, and my course of action has been to accept provisionally the diagnosis of pulmonary tuberculosis and to begin at once to verify it. I have told you of a few of my mistakes in physical diagnosis; I have narrated briefly cases of Hodgkin's disease, of pulmonary tumor, of cardiac disease, of lues, and several others. As I look back over them I see that my errors have been largely of omission. I knew, but I failed to act. I am convinced the greater number of mistakes in diagnosis are due to carelessness, "lack of time," "a cold room," "during another visit"—is how we put it. It is impossible, I believe, for anyone to practise long without making some mistakes and I have a rule of practice which I often repeat to myself: Whenever for a few weeks you escape making a bad mistake, expect very shortly to be guilty of some glaring blunder.

OBSERVATIONS ON THE PROTECTIVE ENZYMES OF THE BODY (ABDERHALDEN).¹

By ERNEST G. GREY, M. D., Boston.

(From The Laboratory of Surgical Research, Harvard Medical School.)

A study of the Abderhalden protective enzymes of the body was undertaken about a year and a half ago, with the view of

¹I wish to express my greatest appreciation to Prof. Cushing for encouraging this work and for the necessary means with which to carry it out. I desire also to thank Drs. Louis Weed, Paul Wegfarth and I. Chandler Walker for frequent aid in supplying me with materials.

ascertaining their relationship to epithelial transplants. As it was necessary to be familiar with the reactions of such ferments and numerous tissues in the body, a number of different organs were prepared, following the specifications laid down by Abderhalden. Specimens of sera were gathered also from different clinical sources. Various combinations of these were then dialysed and in each case the endeavor was made to ad-

TABLE I.

Case No.	CLINICAL DIAGNOSIS.	Placenta, human.	Placenta, dog.	Placenta, cat.	Kidney, human.	Kidney, dog.	Kidney, cat.	Thyroid, normal.	Thyroid, Basedow.	Thyroid, adenoma.	Thyroid, dog.	Ovary, cystic.	Ovary, normal.	Liver, human.	Liver, dog.	Liver, cat.	Pancreas, human.	Pancreas, dog.	Adrenal, human.	Adrenal, dog.	Muscle, human.	Muscle, dog.	Myoma.	Blood, human.	Carcinoma, scirrhus.	Carcinoma, glands.	Adeno-carcinoma.	Hypophysis, beef.
17	Epilepsy.....							0	0															0	0			
4	Lacerated cervix.....												0								0		++					
14	Carcinoma, stomach.....													+											0			
18	Varicose veins.....																							0	0			
36	Pregnancy, 5th month.....	+										0												0	0			
13	Pregnancy, 5th month.....	+																			0	0				+		
11	Pregnancy, ? month.....	0		0																								
	Pregnancy, 3 weeks later.....	+	++	++																								
21	Cardio-renal syphilis.....				±									+			0											
43	Perirectal abscess.....							0	0	0													++					
20	Primary optic atrophy.....							0	0								0										0	
10	Pregnancy, 6th week ?.....	++																				0				0		
19	Suspension uterus											0					0				0		++					
18	Cardiac.....	0						0		0																		
40	Ureteral caruncle					0	0								0	0												
8	Salpingitis, arthritis—gonorrheal.....												0					0					0					
41	Varicose veins.....	0	0	0																								
42	Fistula in ano	0	0	0																								
31	Pregnancy ?	0		+												0												
22	Plastic operation, axilla.....	0																0					+					
25	Pregnancy, 3d month.....	+		++												0												
33	Sarcoma tonsil	0		0						0															0			
30	Varicose veins.....	0																			0							
16	Dyspituitarism												0		0			0									0	
15	Abdominal adhesions.....	0												0			0				0							
51	Basedow's disease				0			++	+				+															
53	Cardiac syphilis.....				0									0			0				0							
27	Pregnancy, 3d month ?.....	+++	++	+++															0									
60	Diabetes.....				0												0	0										
69	Hysteria, internal gland disturbance.....				0			±		0			+															
24	Thyroid struma, Basedow ?.....							0	0	±	0		0															
28	Pregnancy, 2½ months ?.....	+			0									0							0							
68	Varicose veins.....				0										+	+					0							
35	Hypophysis tumor.....	0						0		±																	++	
50	Myomata	0												0								0						
34	Adeno-carcinoma cæcum	0		0																				±		++		
49	Chronic nephritis.....				0			0						0			0											
29	Pregnancy, ? month.....	++				0															0						0	
7	Cardio-renal.....	0			0									0									0					
70	Carcinoma, cervix.....	0		±																				0		++		

TABLE I—Continued.

Case No.	CLINICAL DIAGNOSIS.	Placenta, human.	Placenta, dog.	Placenta, cat.	Kidney, human.	Kidney, dog.	Kidney, cat.	Thyroid, normal.	Thyroid, Basedow.	Thyroid, adenoma.	Thyroid, dog.	Ovary, cystic.	Ovary, normal.	Liver, human.	Liver, dog.	Liver, cat.	Pancreas, human.	Pancreas, dog.	Adrenal, human.	Adrenal, dog.	Muscle, human.	Muscle, dog.	Myoma.	Blood, human,	Carcinoma, scirrhus.	Carcinoma, glands.	Adeno-carcinoma.	Hypophysis, beef.
44	Myomata	0				0												0				0						
26	Pregnancy, 2d month?.....	++		++									0	0														
45	Chronic appendicitis.....	0	0	0																								
46	Polyarthrititis	0																			0			+			0	
23	Healthy.....	0											0								0			0				
54	Abortion 8 days previously.....	0																		0		0						
62	Carcinoma cervix, diabetes.....	+															0								0	0		
5	Hypophysis, polyglandular							0			0	0															0	
2	Pregnancy, 2d month?.,.....	+		++											0									0				
3	Diabetes, coma.....				±												0							±			0	
47	Endometritis							0	0	0																	0	
81	Amenorrhea, hypopituitarism.....							0		0			0														0	
82	Carinoma, breast, metastases.....				0									0					0								+	
48	Abdominal adhesions.....							0			0																0	
6	Pregnancy, 2d month?.....	+		+											0													
38	Cirrhosis, liver	0			0									0					0									
37	Necrosis, phalanx toe.....												0	0							0		0					
12	Not pregnant?.....	0		0											0												0	
39	Carcinoma, cervix	0											0													0	0	
32	Chronic appendicitis.....					0				0																		
55	Pregnancy, time?.....	+									0									0								

TABLE II.

Dog Serum No.	Serum alone before operation.	Serum and liver before operation.	Serum removed.	Serum alone after operation.	Serum and human placenta.	Serum and dog liver.	Serum and cat liver.	Serum and human liver.
1	15 days after transplantation	0	0	0
2	0	0	3 days after transplantation	0	0	+	+	..
3	0	0	5 days after transplantation	0	0	+	±	±
4	0	0	5 days after transplantation	0	0	+	+	±
5	0	0	3 days after transplantation	0	0	++	++	+

here closely to the Abderhalden technique. Some of the earlier work was performed in cooperation with Dr. Alfred Luger, to whom I am indebted for assistance at that time. It was during this period that varying results were obtained, and an interest and lively scepticism arose regarding the specificity of such ferments. Since then some investigators, notably Heilner and Petri² have published similar findings and have placed themselves on record as opposed to the specificity doctrine.

² Heilner u. Petri, Münch. med. Wchnschr., 1913, Vol. LX, 1530.

As the study progressed, however, it was found that the more exactly the experiments were performed and the greater the precautions taken against errors the more specific the ferments appeared.

Since the specimens of blood came largely from the variable clientele of a surgical clinic, no attempt was made to develop a series of cases concerning one or more definite pathologic or physiologic states. The table (No. 1) appended here presents concisely the results obtained in a more or less heterogeneous group of cases. A brief outline of the technique is

given also, together with certain conclusions drawn from the earlier portions of the work.

The method used was that described by Abderhalden. Tissues as fresh as possible were cut into small pieces and washed with 0.8 per cent NaCl solution. They were then boiled in distilled water containing a trace of glacial acetic acid and changed and boiled in distilled water until a negative ninhydrin reaction resulted.

Before each separate test the amount to be used was again boiled in ten times its volume of distilled water and the filtrate tested with ninhydrin. About 2 gm. of the organ and $1\frac{1}{2}$ cc. of hemoglobin-free serum were used. These were incubated for 18 hours at body temperature.

The membranes were carefully standardized, using the same serum and peptone solution for each set. Occasion was taken to frequently retest such sets. Care was exercised to use only perfectly clean utensils.

Manifold errors in the first months of work demonstrated the following points: It is essential that the organs be fresh; great care is necessary in standardizing the membranes and in retesting the sets frequently; it is absolutely necessary that the organs be blood-free; paradoxical results appear to indicate some error of technique such as undoubtedly crept into the investigations of Heilner and Petri; the serum must be hemoglobin-free, fresh and sterile, and collected several hours after meals; a non-specific cleavage of the protein in question usually depends upon the presence of blood corpuscle elements; liver, for example, is very hard to prepare free from blood; controls are necessary for each serum and for each organ. Observing the above precautions such controls have always been negative.

As yet we are not familiar with the part played by acute and chronic inflammatory processes in stimulating or hindering the formation of the ferments under discussion. Thus far we do not clearly understand the part played by polyglandular and polyvisceral disturbances in the formation of antiferments.

Thirty-seven sera from a variety of patients were tried with placental tissue. Twenty-two were from women not pregnant, and of these no serum reacted positively. There were twelve sera from women clinically pregnant. The tests were all positive in these cases with two exceptions. One serum, No. 31, was from a questionable case of pregnancy. It reacted strongly with cat placenta, but not with the human material. The error possibly lay with the placental preparation, which was immediately discarded and new material prepared. Another serum, No. 11, gave a negative test at first, but three weeks later broke down the same placental preparations—human and cat. Four sera from carcinoma cases were set up with placenta. Only one, No. 35, gave a feebly positive reaction.

With kidney tissue from man, dog or cat, sixteen different sera were tried. Of these four had nephropathic histories. No. 21, a cardio-renal case, with syphilis, and No. 3, from a patient in diabetic coma, gave slightly positive reactions. Another cardio-renal, No. 7, and a case of chronic nephritis, No. 49, did not react at all. No. 53, from a cardiopathic patient, gave a negative reaction.

Sixteen sera were tested with normal human thyroid. No. 69, from a case of probable internal glandular disturbance, gave a feebly positive reaction. With Basedow tissue 6 sera were used. Four had no clinical histories of thyroid disturbances. No. 51 was from a case of outspoken Basedow disease and definitely broke down the tissue. It did not affect normal thyroid. No. 69 (see above) yielded a negative test. No. 24, from a nervous patient with a struma, reacted negatively. Ten sera were tried with prepared adenomatous thyroid tissue. Of these three gave some result. No. 24 (see above) and No. 35 (hypophysis tumor) yielded feebly positive results. No. 51 (see above) definitely broke down the adenomatous tissue.

Three sera were tried with dog thyroid. All gave negative tests.

With normal human ovary twelve sera were used. Three of the tests resulted positively: No. 24, thyroid struma; No. 51, Basedow disease; and No. 69, probably internal glandular disturbances. Three sera were used with tissue from a cystic ovary. Only one, No. 36 (pregnancy), reacted—feebly positive.

With tissue preparations from human, dog and cat livers twenty sera were tried. No. 21 (cardio-renal with syphilis), No. 14 (carcinoma of the stomach with marked liver necroses), and No. 68 (varicose veins) yielded positive results. Four of the negative sera—Nos. 25, 26, 28 and 6—were from pregnant cases. Two sera—Nos. 14 and 82—came from patients with carcinoma. The first reacted and the second did not. The donor of serum No. 38 had cirrhosis of the liver with ascites.

Ten sera were set up with preparations of normal pancreas tissue. Two were from nephritic cases and three from diabetic patients—one in coma. In no instance was the tissue broken down.

Adrenal gland preparations were used with nine sera. The tests were all negative.

In thirteen different cases (three pregnant sera) there was no serum which acted upon muscle tissue preparations.

Six sera were used against myoma tissue. Two cases—Nos. 44 and 50—had uterine myomata. In no instance was there a positive reaction.

Ten sera were tried against preparations of human blood. The positive reacting specimens were: Nos. 46 (polyarthritis); 43 (perirectal abscess); 19 (24 hours after a laparotomy); 22 (6 days after plastic operation on axilla); 4 (24 hours after curetage and repair of cervix); and 3 (diabetic coma) feeble reaction.

With preparation of adeno-carcinoma of the caecum ten sera were used. Of these five had clinical (and pathological) carcinoma. Three yielded positive results. Two, Nos. 39 and 62 (from carcinoma cases) gave no reaction. Six sera were tested with lymph gland metastasis preparations. All resulted negatively. Two of these, Nos. 39 and 14, were from patients with carcinoma. One serum, No. 33, was from a case of carcinoma of the tonsil. Six sera with a scirrhus carcinoma preparation (from the breast) yielded negative results, except one case, No. 34, which was feebly positive.

A beef hypophysis preparation was set up with eight sera. Of the latter, four were from dyspituitary cases. Three were negative (Nos. 5, 20 and 16). One reacted positively (No. 35).

BLOOD FERMENTS FOLLOWING TRANSPLANTATIONS.

In December, 1912, a case in the surgical service of the Johns Hopkins Hospital was operated upon—sellar decompression—for an hypophyseal cyst. The patient manifested a syndrome of hypopituitarism, with accompanying diabetes insipidus. Several months later, because of the marked pituitary insufficiency, a second operation was undertaken, consisting of a subcortical implantation of the hypophysis of a newborn child. Improvement in the glandular signs appeared for a short time. Subsequently, however, the features of the hypopituitarism became marked, and the patient finally succumbed.

The improvement noted was attributed by the operator to either the material contained in the glandular transplant or to the secretion manufactured by the transplant itself during its period of absorption. Could the graft have survived indefinitely it seemed plausible that the patient might have recovered, in part at least, from the state of hypopituitarism.

Similar negative results were obtained by Exner³ in transplanting the hypophysis in rats.

The laws governing the viability of epithelial transplants are still very obscure, in spite of much work in this direction. The literature yields opinions, however, nearly unanimous in the view that homo- and hetero-transplants of the parathyroid gland are absorbed ultimately as foreign material.⁴ Halsted's⁵ dog, which maintained good health with a parathyroid autograft approximately $\frac{1}{4}$ mm. in diameter, is a striking example of its kind.

In brief we may mention the following as some of the possible factors in the failure of such transplantation work.

1. A "Verhungern" of the transplant.⁶
2. A toxic action of the transplant on the host. Such a condition is found in certain cases of blood transfusion.⁶
3. A toxic action of certain constituents of the hosts plasma upon the graft.⁷
4. The lack of a necessary degree of deficiency in the host, of the gland in question.⁸
5. A trophic sequence.
6. An immunity reaction—in the sense of an anaphylactic reaction,⁹ or otherwise.

The fact that at first the transplants frequently become vascularized and only later are absorbed argues against a permanent interference with the blood supply in all cases.

Carrel's¹⁰ work on the kidney has shown that such an organ may survive transplantation in the same animal and functionate, provided the circulation be maintained. This, in part, answers the fifth point above, namely, that certain glands can probably functionate successfully without their nerves and after a temporary suppression of their special secretory duties.

The second, fourth and sixth points may be considered under the heading of a "defensive mechanism," in the sense of Murphy¹¹—a mechanism whose strength and rapidity of reaction depend upon the degree of relationship, being more prompt and violent the more foreign the tissue introduced. Murphy thinks that this defensive mechanism is a property developed rather than one naturally present in the host.

Russell¹² has shown that the cells of a mouse survived and multiplied in a normal rat for more than nine days, while in a rat previously immunized the graft was rapidly disintegrated. Furthermore, Lambert and Hanes¹³ have added the observation that rat and mouse tissues will grow almost as well in plasma from an alien as from the native species. If the animal, however, from which the plasma is obtained is previously immunized with the living cells of the foreign species, the plasma will inhibit or actually prevent any such activity.

In view of the protective ferment mechanism of the body demonstrated by Abderhalden in other fields, the observations above mentioned suggested a possible cytolytic action on the graft of antienzymes developed in the host following the transplantation. It appeared conceivable that the hypophyseal graft considered above caused the formation of proteolytic enzymes which, in turn, brought about its ultimate absorption. As the patient had previously received glandular therapy, both intravenously and by mouth, we are able to conceive how such glandular administration may have lessened the chances for the ultimate survival of the foreign pituitary body.

With this idea in mind an endeavor was made to use the Abderhalden technique in detecting such antiferments as might be present after the transplantation of an epithelial organ. The liver was chosen because of its size and ease of access. As the accompanying table (No. 2) shows, five dogs were used in the experiment. In each case, with one exception, the animal was bled previous to the transplantation and the serum tested for ferments capable of breaking down liver protein. It was negative in each case. In the first dog—the exception—a preliminary test was not made, but since the ultimate result proved negative, this has no significance.

In Dog 1 a small piece of liver, roughly 7 or 8 gm., from another dog just sacrificed, was implanted under the rectus muscle. The wound healed *per primum*. Fifteen days after the operation the blood serum was tested against dog liver. The result was negative. The length of time lapsing between the transplantation and the test and the method of grafting

³ Exner, A.: Deutsche Ztschr. f. Chir., 1912, CVII, 172.

⁴ Leischner, H., and Köhler, R.: Arch. f. klin. Chir., 1910, XCIV, 169.

⁵ Halsted, W. S.: J. Exp. Med., 1912, XV, 205.

⁶ Schöne-Marburg: Wien. klin. Wchnschr., 1911, XXIV, 734.

⁷ Axhausen, G.: Med. Klinik., 1911, VII, 1801.

⁸ Halsted, W. S.: J. Exp. Med., 1909, XI, 175.

⁹ Schöne-Marburg: *loc. cit.*

¹⁰ Carrel, Alexis: J. Exp. Med., 1910, XII, 146.

¹¹ Murphy, J. B.: J. Exp. Med., 1913, XVIII, 491.

¹² Russell, B. R. G.: Third Scientific Report of the Imperial Cancer Research Fund, 1908, 341.

¹³ Lambert, R. A., and Hanes, F. M.: J. Exp. Med., 1911, XIV, 129, 453.

the liver tissue were held accountable for the failure in this experiment.

In Dog II about 15 gm. of liver were removed from a recently killed dog, cut into small pieces and implanted under the rectus muscle. Three days later the serum was set up with dog and cat liver tissue. They both reacted positively.

In Dog III about 15 gm. of liver were removed from a dog, cut into very small pieces and implanted under the rectus muscle of the donor. After five days the serum was tested for proteolytic ferments. It reacted with dog, human and cat livers.

In Dog IV about 15 gm. of liver were removed as in Dog III, cut into fine pieces and transplanted under the rectus muscle of the same animal. With dog, cat and human liver preparations the serum reacted after five days.

In Dog V about 10 gm. of liver tissue ground up in salt solution (from another dog) were injected intraperitoneally. Three days later enzymes were present in the dog's serum capable of breaking down dog liver.

Human placenta was used as a control in these dialysations. Such controls were always negative.

These results seem to indicate that liver tissue, under certain circumstances, when transplanted into a dog, acts as foreign protein in the animal's circulation and stimulates the formation of proteolytic enzymes capable of digesting it. Transplants of this nature, then, have to cope with protective ferments developed in the body of the host.

Between the experiment as carried out in Dogs II, III and IV, and the experiment represented by Dog V there is no essential difference other than one of quantity. Where the gland tissue has been reduced to a semi-fluid form we expect it to have a greater capacity for stimulating the formation of

antienzymes than an equal mass of gland tissue sectioned into pieces. Just so a transplant of less proportions, an hypophysis for example, probably brings about a protective ferment formation of comparatively limited extent, a formation entirely commensurate with its size. There is every reason to believe then that the process is the same in each case. From these considerations we are fairly safe in concluding that a small graft as well as a larger one is capable of stimulating the formation of a protective mechanism in the body of the host.

Since the subcutaneous,¹⁴ intraperitoneal,¹⁵ and oral administrations¹⁶ of protein all stimulate the formation of ferments capable of breaking down such a protein into its cleavage products, it is clear that procedures of this nature, if instituted before or during a transplantation, will serve to aggravate the antiferment formation evoked by the graft itself.

CONCLUSIONS.

1. The results of this work agree with the conclusions of those investigators who have found that the Abderhalden ferments are specific.

2. In transplanting epithelial organs it is necessary to remember that such a procedure stimulates the formation of antiferments in the host; and, in the case of glands, it is important to avoid any preliminary intravenous or subcutaneous feeding—perhaps oral also—of the substance, since such administrations encourage the development of protective enzymes on the part of the host.

¹⁴ Frank, E., u. Rosenthal, F.: München. med. Wehnschr., 1913, LX, 1594.

¹⁵ Fuchs, A.: München. med. Wehnschr., 1913, LX, 2230.

¹⁶ Bauer: Wien. klin. Wehnschr., 1913, XXVI, 1109.

PRINCIPAL TYPES OF MICRO-ORGANISMS IN BALTIMORE MILK.

By L. P. SHIPPEN, M. D.

(From the Laboratory of Hygiene and Bacteriology, Johns Hopkins University.)

During the past year an attempt has been made to describe and classify the most frequent and important organisms found in Baltimore milk. The studies on pasteurization now being made in this laboratory, and the attempt to demonstrate the ætiological relationship between certain intestinal infections, notably typhoid fever and the summer diarrhœa of children, and an impure milk supply, render such a study of great importance, as it is manifestly impossible to determine the fate of pathogenic organisms or to explain the effect of heat of various degrees on milk without some notion as to the bacteria which predominate in the milk in any given community.

The organisms which we have encountered have been described as far as possible in such a way that their identification by other workers in this field may be comparatively easy. No great care has been expended upon descriptions of colonies in agar or gelatin, or the manner of growth of the organisms in these media, on shades of pigment, or upon a number of other properties of bacterial growth which are variable, and depend

on inconstant properties of the media employed, and which are frequently of so elusive a nature as to be incapable of description. On the other hand stress has been laid upon those biological activities which are usually constant, and whose presence or absence may be indicated by positive or negative characters.

The samples of milk examined were collected from small shops in the northeastern part of the city, with the exception of two specimens obtained in bottles from local dairies. Plates of agar were poured at once and the predominant colonies picked up after twenty-four to forty-eight hours incubation at 37° C. The samples of milk were also incubated for twenty-four hours, and a second set of plates made from which colonies were also picked. When for any reason there arose suspicion of a mixed culture, plating was again resorted to, or whenever the colonies were so numerous that there seemed danger of transferring a mixed culture, the colonies themselves were again plated, and well separated colonies transferred to agar.

The organisms from these agar growths were then inoculated into litmus milk, gelatin, potato and neutral broth, and into dextrose, lactose, and saccharose broth in fermentation tubes. With certain organisms which failed to grow well in broth, agar, to which the various sugars were added, was substituted for the fermentation tubes. Of the media mentioned potato was found to be of the least value from the standpoint of constancy and clearness in description, but was used throughout because of its importance in a few instances, and out of regard to former descriptions.

Only twelve different samples of milk were studied, since no attempt was made to isolate and describe all the rarer bacteria existing in milk, and it was found that the common types were encountered in the first few specimens examined. The later samples revealed the same organisms, or variants of the same differing in no very important details. About forty different strains were isolated, and we believe that these include the most common varieties of bacteria existing in Baltimore milk.

The organism most frequently encountered, and the one which seemed to exist in the greatest numbers corresponded to a type described by Günther and Thierfelder,¹ Leichmann,² and others as a bacterium, and by Grotenfeldt³ and others as a streptococcus, and which is commonly known as *B. acidi lactici*, *Bact. lactis acidi*, and as *Streptococcus lacticus*.

Great confusion exists in regard to this organism on account of the fact that different investigators have given it various names, while others have given a similar name to a distinct, separate species. Thus Hueppe⁴ has named *B. acidi lactici* an organism which grows like *B. coli*, produces gas in dextrose, forms spores, and peptonizes milk, and Grotenfeldt³ and Zopf⁵ independently have described bacteria indistinguishable from *Bact. ærogenes* and *B. coli* which they have called *B. acidi lactici*, and Perkins⁶ has taken this type, and made it a definite subdivision of the Friedländer group. At the present time the term *B. acidi lactici* has very little meaning. If used at all it should apply undoubtedly to the organism described by Hueppe, which grows luxuriantly on agar, and forms gas in dextrose, and which according to some authors is in reality *Bact. ærogenes* (Escherich) Migula, and which according to Perkins differs from the latter only by its inability to ferment saccharose.

The other type which is the predominant one in the Baltimore milk, also sometimes known as *B. acidi lactici*, grows very faintly on agar, produces no gas in dextrose, and according to some authors is a bacterium, and in the opinion of others is a streptococcus. Günther and Thierfelder^{1,c} first described it, but erroneously identified the organism with the one previously described by Hueppe. Leichmann^{1,c} first recognized the difference between the two, but very unfortunately named the organism *Bact. lactis acidi* in contradistinction to the *B. acidi lactici* of Hueppe. The similarity of these two names, and the fact that Günther and Thierfelder had identified the bacterium, later called *Bact. lactis acidi* by Leichmann, as the *B. acidi lactici* of Hueppe resulted in endless confusion, many authors continuing to apply the latter term to the organism which should bear the former appellation.

To make matters worse, other observers described apparently the same bacterium, but called it by various names. This is well shown by the fact that Matzschita⁷ regards the terms *Bacterium güntheri*, *Bacillus lactis acidi* Liebmann, *Bacillus der spontanen Milkgerinnung* Günther and Thierfelder, as synonyms for *Bacillus lacticus* (apparently the *Bacillus lacticus* of Kruse⁸), and states that the *Bacillus leichmanni* (*Bacterium lactis acidi*, *Milchsaurebacillus* of Leichmann) is probably identical with it.

In addition, the curious morphology of the *Bact. lactis acidi* of Leichmann made the situation even more involved. For it is evident from the literature that there exist either two organisms of identical cultural characters, one a bacterium, the other a streptococcus, or else that the morphological appearance of a single organism has been differently interpreted by various observers. Thus Leichmann^{1,c} named the bacterium of Günther and Thierfelder *B. lactis acidi*, and Liebmann,⁹ Kozai,¹⁰ Utz,¹¹ Esten,¹¹ and Schierbeck¹² seem also to have described the same organism as a bacterium. But Kruse¹² called attention to the resemblance which it bore to the pneumococcus, and suggested that a better term would be *Streptococcus lacticus*, though he acknowledged that rod-shaped forms existed.

Then Grotenfeldt,^{1,c} Weigmann¹³ and Freudenreich¹³ described streptococci which seem identical with this *Streptococcus lacticus* of Kruse, and finally Marpmann¹⁴ named apparently the same organism *Sphærococcus acidi lactici*.

The name *Streptococcus lacticus* given by Kruse has been generally adopted, and has found its way into various textbooks, but has the serious disadvantage of ignoring the bacterial form, and of placing the organism definitely in the class of streptococci, thus raising the question of its relationship to the *Streptococcus pyogenes*. On this account and in order to avoid the use of the term *Bact. lactis acidi*, which has been the cause of so much confusion, the writer in this paper has substituted the name *Bact. güntheri*, used first by Lehmann and Neumann in May, 1896, to designate the organism described by Günther and Thierfelder,^{1,c} but incorrectly identified by them as the *B. acidi lactici* of Hueppe. According to the rules of nomenclature this term should take precedence over the name *Bact. lactis acidi* later given to the same organism by Leichmann, and to the names *Bacillus lacticus* (Flügge^{1,c}) and *Streptococcus lacticus*, also later applied by Kruse.

Some strain of this bacterium was isolated from every specimen of milk examined. Usually it was found as the predominant type in curdled milk, but not uncommonly it seemed to be the most numerous variety in fresh milk as well.

In regard to morphology and cultural reactions, the writer's results differed in no important detail from the description given by Kruse. The organism when examined in a hanging drop made from a 24-hour dry agar slant culture presented an appearance which varied in different cultures. Some strains were composed of slender, short rods. In others the shape and size were so dissimilar that the appearance was that of a mixed culture, as has been noted by Bartlett.¹⁵ For some of the forms were broad, some slender; some had pointed ends, others had ends rounded; some were so short as to closely resemble cocci; others were two or three times as long as broad. Single forms,

pairs, short chains and clumps all added to the picture of a contaminated culture. But repeated platings failed to change this appearance, so that it is evident that but one organism was present.

On the other hand other strains when examined in the same way seemed at first glance to be genuine diplococci or streptococci, and at first the writer thought it possible to classify the various cultures into two distinct types, one a polymorphous bacterium, the other a streptococcus. But careful search always revealed streptococcus forms in the bacterial type, and bacterial forms in the streptococcus type, while so many strains were intermediate in character that finally the writer was forced to the conclusion that no definite line could be drawn between the two varieties.

When examined in smears stained with gentian violet the likeness to streptococci became even more marked. The rod-shaped forms under these conditions appeared mostly as diplococci, and as noted by Kruse resembled closely the pneumococcus. In milk the various strains also appeared as diplococci and as short streptococci, and in plain broth and in the sugar broths long chains were frequent.

All of the strains isolated agreed in growing faintly on meat extract agar, in producing no hæmolysis on rabbit blood agar, in being Gram positive, in showing no motility, nor capsules, nor spores, and in being facultative anærobic, growing even better in the stab than on the surface of agar. In addition, they grew at a temperature of 20° C. as well, though more slowly than in the thermostat at 37° C. This important fact was early recognized by Kruse^{1.c.} in his discussion of the relationship of this organism to the pneumococcus.

The colonies in agar appeared at the end of twenty-four to forty-eight hours in the thermostat as minute pin points and pin heads, which, under the microscope, appeared homogeneous and translucent. Some strains grew in broth in the form of a flocculent precipitate without turbidity, while others produced a faint cloudiness in this medium. On potato there could be observed at times a barely perceptible growth; at other times no visible reaction could be perceived. None of the strains liquefied gelatin, though they all grew well along the line of the stab. In regard to milk, the action was variable, as has also been noted by Kruse^{1.c.} Sometimes this medium was coagulated with a strongly acid reaction and reduction of the litmus after twenty-four hours in the thermostat. At others only a slight, though permanent, acidity was produced, even at the end of two weeks or more. At first this was thought to indicate definite strains, but it was found that the power of coagulating milk was not a constant quantity with this bacterium. When a culture which possessed this quality was plated, it was observed to give off strains which failed to coagulate the milk, though otherwise identical with the original organism, and one culture which at first failed to coagulate, after several month's growth on agar assumed this power.

The action of the organism upon dextrose, lactose, and saccharose broth was found to vary with its power of growth in these media. But when agar was used as a base the result became constant for each particular strain, and consisted in all

cases in the production of acidity in dextrose and lactose. In saccharose some strains caused acidity, while others did not. No gas was ever observed.

When injected subcutaneously into rabbits and guinea pigs in large doses no apparent harm resulted. A number of guinea pigs and rabbits were thus treated with broth emulsions made by scraping and washing the growths of freshly isolated strains from twenty-four hour slant agar cultures. At the end of four weeks these animals seemed as healthy as ever.

The viability of the organism was tested by transplanting every month from agar slant to agar slant for one year. Under these conditions the organism continued to live, and four strains so kept gave at the end of this period the same reactions as at the beginning. A fifth strain which at first failed to coagulate milk later was able to do so.

The thermal death point of these strains in milk was roughly estimated after nearly a year had passed from the time of their isolation, and strangely enough was not found to be uniform. Thus four of the cultures were killed when transferred to milk and immediately heated in a water bath kept at 60° C. for fifteen minutes. A fifth strain when repeatedly treated under identical conditions survived a temperature of 65° C. for fifteen minutes, but was killed by 70° C. for the same length of time. Morphologically, this latter culture belonged to the streptococcus type of *Bact. g ntheri* and seemed to be otherwise identical with types whose thermal death point was under 60° C. The fact that one strain showed in milk a thermal death point of between 65° C. and 70° C. would indicate that some strains of this organism are capable of surviving pasteurization.

On account of the importance attached by many departments of health to the presence of streptococci, and especially of the *Streptococcus pyogenes* in milk, and because of the resemblance which this organism bears to *Bact. g ntheri*, it may be well to consider here the question of the identity of the two species. Kruse^{1.c.} first called attention to the great similarity existing between the lactic acid bacterium of Leichmann and the *Streptococcus lanceolatus*, and proposed for the former the term *Streptococcus lacticus*. Heinemann¹⁷ in a recent paper states that "the *Streptococcus lacticus* agrees in morphological, cultural, and coagulative properties with pathogenic, fecal and sewerage streptococci," and further concludes that "since *Streptococcus lacticus* is invariably present in market milk, and in fresh milk collected with good precautions, the sanitary significance of streptococci in market milk will need further investigation."

With this latter statement we agree thoroughly, but in our opinion there do exist definite morphological and cultural differences between *Bact. g ntheri* (called *S. lacticus* by Kruse and Heinemann), and the *Streptococcus pyogenes*, which is evidently the organism meant under the term "pathogenic Streptococci." This point is important from a public health standpoint. For if *S. pyogenes* agrees in its morphological and cultural properties with *Bact. g ntheri*, it is evident that the identification of *S. pyogenes* becomes impossible. And since *Bact. g ntheri* is practically always present in milk, even

of high quality, it follows that the isolation of an organism having its cultural and morphological properties ceases to have any sanitary significance.

But according to our observations *Bact. g ntheri* and *S. pyogenes* show the following differential points:

First. Morphologically *Bact. g ntheri* usually presents some rod-shaped forms when examined in a hanging drop made from an agar slant, and some strains show very little resemblance to streptococci under these circumstances. *S. pyogenes* on the other hand is commonly a definite streptococcus under such conditions.

Second. *Bact. g ntheri* never hemolyzes blood agar in our experience. *S. pyogenes* usually does so.

Third. *Bact. g ntheri* lives for at least a month on meat extract agar kept at room temperature. *S. pyogenes* on this medium under these conditions dies in about ten to fourteen days, or even in a shorter period of time, and indeed may not grow at all.

Fourth. *Bact. g ntheri* grows on favorable media at a temperature of 20  C. *S. pyogenes* requires a higher temperature.

Fifth. One of the strains of *Bact. g ntheri* isolated by the writer possesses a thermal death point of between 65  C. and 70  C. *S. pyogenes* has a thermal death point of 54  C. according to Sternberg¹⁸ and Hartmann.¹⁹ At times it may be possible to differentiate the two organisms by this means alone.

Sixth. Some observers state that *Bact. g ntheri* is not pathogenic for rabbits and guinea pigs, although others differ in regard to this. Heinemann²⁰ admits "that streptococci freshly isolated from milk, apart from those originating from mastitis, do not possess high virulence," but claims that this property may be acquired. In the writer's experience *Bact. g ntheri* is non-pathogenic for rabbits and guinea pigs even when inoculated in huge doses from freshly isolated strains. *S. pyogenes* when freshly isolated usually is pathogenic for these animals.

In addition, it should be remembered that much of the confusion existing in regard to the various properties of *S. pyogenes* may arise from the fact that many of the atypical cultures recovered from tonsils, the mucous membranes of the mouth, and other sources touched by milk, with which *Bact. g ntheri* is readily confused, very possibly may be in reality *Bact. g ntheri*, and not the genuine *S. pyogenes*.

If these observations are correct it follows that *S. pyogenes* may be identified and separated from the organism which seems universally present in milk, and which it so closely resembles. In consequence the isolation of a culture having the typical morphology and cultural reactions of *S. pyogenes* should have some significance from a public health standpoint. But it must be admitted that *S. pyogenes* and *Bact. g ntheri* resemble each other so closely in their cultural reactions and morphological features that even after isolation in a pure culture they can be distinguished only after careful study. In addition, the two organisms considered are practically indistinguishable in milk by morphological means, though sometimes presenting minor differences, such as length of chain for-

mation. In consequence, any diagnosis of *S. pyogenes* in milk made solely on the basis of microscopic examination must be very dubious in character.

Next may be described a species which in many ways was very similar to *Bact. g ntheri*, and for this reason is considered here. This organism, which probably may be identified best with the one mentioned by Conn²⁰ as *B. lactici aerobans*, was found three times in fresh milk, and on two occasions seemed the predominant type present. It was a bacillus which resembled the bacterial type of *Bact. g ntheri*, and like the latter sometimes presented the appearance of a mixed culture. At times when examined in a hanging drop made from an agar slant preparation many of the forms seemed to be short, fat rods with rounded ends. Others were so short as to appear circular, and yet others were beyond doubt rather thin bacilli. Short chains were common. Like *Bact. g ntheri* the organism was Gram positive, and possessed neither capsules, nor the power of spore formation. At first it appeared to be non-motile, but after several months growth on agar there was observed a definite rotatory motility quite distinct from Brownian motion, which placed it definitely in the class of the bacilli. Culturally the organism differed from *Bact. g ntheri* by its action on litmus milk, in which it produced no apparent change, and upon lactose agar in which it caused no acidity. Otherwise it was identical with the saccharose fermenting type of *Bact. g ntheri*.

After *Bact. g ntheri*, which is of constant occurrence in Baltimore milk, the most frequently encountered single organism was *Bacterium aerogenes* (Eseherich) Migula l.c. * (*B. lactis aerogenes*). It was present in half the samples of milk examined, twice in fresh, and four times in incubated milk. It is significant that half the specimens did not reveal the organism on the plates, and it is reasonable to conclude that it was either lacking from the samples, or, what is more probable, present in comparatively small numbers, since the colonies of this bacterium are large and well developed on agar plates, and not readily overlooked. The organism had classical morphological and cultural reactions, showing itself under the microscope when stained from a milk preparation as a large encapsulated bacterium, positive to Gram. It acidified and coagulated milk without peptonization, failed to liquefy gelatin, produced gas on potato, and fermented all three of the carbohydrates employed. This organism is now usually classed in the Friedl nder group. It is worthy of note that the corresponding encapsulated bacterium, *Bact. acidilactici* as described by Perkins,^{1,c} was not encountered, all the other fermenting bacteria which were found being probably strains of *B. coli*.

In addition to *Bact. aerogenes* various bacteria connected with the intestinal tract were isolated with a fair degree of regularity. The non-saccharose fermenter *B. coli* (Eseherich) Migula was found in four samples of sour milk, and the saccharose fermenter usually now referred to as *B. coli communior*, according to Durham's suggestion, was found three times in fresh and twice in sour milk. Several of the strains of *B. coli*

* P. 396.

when first isolated were quite devoid of motility, even in 18-hour cultures in broth, and such organisms naturally resembled the *Bacterium acidi lactici* (Perkins) of the Friedländer group. But with the exception of one strain all such cultures developed definite motility after cultivation in the laboratory for a time, and were thus clearly to be regarded as *B. coli*, and the one strain in which no motility was ever demonstrated failed to show any mucoid growth on agar, and at no time could we determine in it the presence of capsules. This culture we came to regard as representing the *B. coli immobilis* of Germano and Maurea,²¹ since it has all the cultural reactions of *B. coli communis* of Escherich, but is devoid of motility. Then an organism which was identified as *B. zenkeri* (Hauser) Migula^{1.c.*} (*B. proteus zenkeri*) was obtained three times, once from fresh and twice from sour milk. This was characterized by branching colonies on agar, and a branching penetrating growth on an agar slant and in gelatin. It was positive to Gram, was motile, and showed no spores. On potato, it produced a dirty brown growth; gelatin it failed to liquefy, and milk it rendered alkaline, without coagulation or peptonization. In dextrose, lactose, and saccharose broth it produced neither acidity nor gas. No characteristic cultures of *B. proteus vulgaris*, nor of *B. proteus mirabilis* were ever isolated.

In addition to these well-marked types, a number of non-pigmented, non-spore bearing bacteria were isolated whose characteristics we usually associate with the organisms of the intestinal tract, and for this reason are described in this paper, although they cannot be said to occur frequently in the Baltimore milk. These bacteria present great difficulty in proper classification. They have doubtless been described by other observers as occurring in milk, but if so the descriptions are too inadequate or indefinite to be made use of. They correspond closely to species described by Ford²² as existing in the intestinal tract, and while the absolute identity of the two sets of organisms, one derived from the intestinal contents, the other from milk, cannot be proven, we prefer to follow the descriptions given by this author. These organisms were as follows: *Bacterium oxygenes*, isolated in one sample of sour milk; *Bacterium cæci*, isolated from one sample of fresh milk, and *Bacillus chylogenes*, which was found as the predominant organism in one sample of milk, both when fresh and sour.

Bact. oxygenes was Gram negative, showed no motility or capsules, and formed no spores. It had the appearance of *B. coli* on agar, produced a luxuriant growth on potato, and made broth turbid. It failed to liquefy gelatin, and coagulated litmus milk with the production of whey and of a pink color that seemed to indicate acidity. Yet neither in lactose nor saccharose broth did it form any acidity or gas. In dextrose broth it produced acidity without gas, and in this differed from the *Bact. oxygenes* of Ford, which made this medium alkaline.

B. cæci like the preceding was Gram negative, formed no spores nor capsules, and showed no motility. But on agar it appeared translucent and moist, and on potato and in broth it failed to grow visibly. It liquefied gelatin slowly, and peptonized milk with an alkaline reaction, and without coagula-

tion. In dextrose, lactose, and saccharose agar it produced neither acidity nor gas. Except in regard to motility this organism corresponded very closely to the *B. cæci* of Ford.

B. chylogenes was of especial interest, since it appeared in large numbers in the one specimen of milk in which it was found, and indeed seemed to be the predominant organism. It was Gram negative, possessed no capsule, formed no spores, and was violently motile. All of its reactions were very slow in forming, appearing only at the end of from three to ten days. On agar the bacillus at first grew faintly, but later resembled *B. coli* in its general appearance. It flourished luxuriantly on potato, and produced turbidity in broth. It liquefied gelatin, and coagulated milk. It produced neither acidity nor gas in lactose and saccharose. In dextrose it formed acidity without gas. It will be seen that this organism corresponds to the *B. chylogenes* of Ford, except for its growth on potato.

Associated with these organisms may be placed a species which occurred in half the samples of milk examined, five times in fresh specimens and once in an incubated specimen. Although it was never the predominant organism, it was a clear-cut variety, with definite cultural reactions, and was comparatively easy to recognize. In its cultural reactions it closely resembled the *B. faecalis alkaligenes* of Petruschky, from which it differs in regard to motility, morphology, and Gram reaction. It also resembled the organism described as *B. No. 66* by Conn^{1.c.*} and the *B. Troilii* (*Bact. lactis longi* b) mentioned in Matzschita,^{1.c.†} with which perhaps it may best be identified.

Examined in the hanging drop this organism appeared as a rather fat bacterium, about twice as long as broad, with rounded ends and without motility. No capsule was demonstrated. When stained by the Gram method it retained the gentian violet. On agar its growth resembled closely that of *B. coli*. Its colonies in this medium after twenty-four hours incubation appeared as minute pin points and pin heads, opaque when deep, delicate and translucent on the surface. However, in forty-eight hours these grew to be quite large, and were often indistinguishable from those of *B. coli*. In gelatin and on potato it likewise resembled *B. coli*, causing no liquefaction of the former medium, and forming a moist, heavy, brownish growth on the latter. But in milk and in the sugars employed its action was quite different. In these media it produced no acidity. No gas was formed in dextrose, lactose or saccharose, and litmus milk inoculated with this organism gradually became more and more alkaline, but was never peptonized, or coagulated. In meat extract broth it usually failed to grow, although one strain succeeded in producing a slight turbidity in this medium.

A variety of this bacterium was found on three occasions in fresh milk. It differed from the more common type in producing acid in dextrose, and in causing no visible growth on potato.

The most difficult organisms to classify satisfactorily, and a

* P. 816.

* P. 54.

† P. 376.

group encountered with great frequency, being in fact next to *B. leichmanni* in this respect, were the various species of micrococci. By far the larger number resembled closely the pyogenic staphylococci, from which often they could be differentiated only by their manner of growth on agar, a characteristic very difficult to describe clearly. The various strains belonging to this type differed but little in cultural reactions, and could be included in one group whose various members are apparently identical with the organism described by Zimmerman²³ from water (*Micrococcus cremoides*), and by Dyar²³ from air (*Micrococcus aureus*). For convenience of description, they will be placed in one group, which will be named after the coccus first isolated by Zimmerman (*M. cremoides*).

One or more members belonging to this general type were isolated from ten specimens of fresh milk out of the twelve examined, but were never the predominant organism, though occasionally occurring in large numbers. The different strains agreed in being Gram positive, and often showed a variation in size and in intensity of color when stained with the ordinary aniline dyes. It was not unusual to see in a smear from a fresh, carefully plated culture forms so markedly different in size and in depth of staining that it was impossible to believe in the purity of the preparation. Yet invariably subsequent plating failed to change this appearance. At the present time, after several months growth on agar, this peculiarity has disappeared, and only rather large staphylococci are found in the cultures.

The various strains appeared on agar plates as large, coarse, opaque, white or yellowish colonies. On agar slants they grew luxuriantly, at first white, but later often turning to a dirty yellowish tinge, the agar itself assuming a brownish color. In gelatin liquefaction along the line of the stab was produced in from forty-eight hours to ten days, while on potato there usually appeared in twenty-four hours a flat, white or yellowish growth, at times faint, at others profuse, probably dependent upon some unknown factor in the ingredients of the potato.

In milk the different members of the group varied somewhat, for while the majority acidified and coagulated the medium with the expression of so much whey that peptonization was suggested, and may indeed have been present, yet others produced only a soft acid coagulum, with little or no whey.

All of the types formed acidity without gas production in dextrose and lactose agar, but in saccharose, while some produced acidity in twenty-four hours, others failed to do so after seven days incubation.

The only other coccus found more than once during the course of the examination showed tetrad forms, and could be classed with the sarcinæ. It closely resembled the preceding group in its manner of growth on agar and in its general cultural reactions, but differed somewhat in its action on milk and gelatin. The former medium it acidified, but failed to coagulate, while gelatin it liquefied in the form of a cup, rather than along the line of inoculation, as was the case with *M.*

cremoides. It was recovered three times from fresh milk, and so possibly may be classed among the more common organisms, but could not be identified with any accuracy with any sarcina forms previously described and named by other observers. For this reason and on account of its close resemblance to the *M. cremoides* type, the writer has preferred to place it as a sub-variety of this group.

The organisms just described probably include the most common species existing in the Baltimore milk, capable of growing aerobically at body temperature on ordinary media. But in addition, there were encountered a number of classified and unclassified cocci, bacteria, spore bearers, and yeasts similar to those found in the air and water. Their occurrence was inconstant, and they were present usually in small numbers. Each specimen of milk examined revealed one or more new varieties, but it was felt that their rarity and scarcity made their detailed description a matter of little value. However, it is worthy of note that on two occasions yeasts seemed to be the predominant type in curdled milk, being apparently more numerous than *Bact. g  ntheri*, and that one of these forms, though the predominant type in curdled milk, yet failed after isolation to produce any but an alkaline reaction upon this medium.

This yeast grew rather faintly upon agar, produced no pigment, and was Gram positive. It failed to liquefy gelatin, and made milk alkaline in much the same way as *B. alkaligenes*. In dextrose and saccharose broth it produced acidity and gas, which consisted almost entirely of carbon dioxide. In lactose broth neither acidity nor gas was observed.

The other variety of yeast occurring in large numbers in one sample of curdled milk was identical with the preceding, except for its action upon lactose and milk. The latter it acidified and coagulated, while in lactose broth it produced both acidity and gas.

CONCLUSIONS.

1. The most frequently encountered organism in the milk of Baltimore belongs to the type described by some as a bacterium, by others as a streptococcus, and which is variously known as *B. acidi lactici*, *Bact. lactis acidi*, *Bact. lacticus*, and as *S. lacticus*. In the writer's opinion, *Bact. g  ntheri*, a term first used by Lehmann and Neumann, is the correct name.

2. Certain strains of *Bact. g  ntheri* closely resemble *S. pyogenes*, but in our opinion may always be differentiated from this coccus.

3. Certain strains of *Bact. g  ntheri* possess in milk a thermal death point of between 65   and 70   C. and so are theoretically capable of surviving pasteurization.

4. *Bact.   rogenes* (Escherich) Migula (*B. lactis   rogenes*), and the various strains of *B. coli*, next to *Bact. g  ntheri*, were the organisms most frequently met with. They are more easily recovered from curdled milk, but are also frequently isolated from fresh samples.

5. No *B. acidi lactici* of the Friedl  nder type was encoun-

tered during the examination, and it seems possible that this organism described as occurring frequently in milk may correspond to the *B. coli immobilis* of Germano and Maurea.

6. Other organisms resembling *B. coli* in many ways may be isolated from time to time, and sometimes are the predominant type in the sample of milk collected. Their identification presents great difficulties. For the sake of clearness they have been regarded and described as identical with some of the rare organisms found in the intestines.

7. A bacterium resembling *B. alkaligenes* in its cultural reactions, but perhaps best spoken of as *Bact. Troili*, is quite common in fresh milk in this vicinity.

8. The micrococci in milk are found in such great variety that any satisfactory classification is difficult to make. The majority may be grouped together as the cremoides type first described by Zimmerman. They are organisms apparently derived from air and water, and usually are recovered from fresh milk.

9. The remaining organisms isolated, while presenting interesting features in special cases, are too inconstant and usually too few in number to make their description a feature in a paper of this character.

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BACTERIOLOGICAL FINDINGS IN BALTIMORE OYSTERS.

By MORRIS JOSEPH, B. S.

(From the Laboratory of Hygiene and Bacteriology, The Johns Hopkins University.)

While but a few cases of typhoid fever have been traced with clearness to the use of oysters contaminated with sewage—such cases occurring, as a rule, in epidemic form as reported by Conn¹—the opinion has been gaining ground that much of our winter typhoid fever has its origin in sewage-polluted bivalves. This opinion is strengthened by the careful study of the occurrence and distribution of the cases of typhoid fever in such a city as Washington. The recent observations of Gorham,² however, throw some doubt upon the wisdom of attributing winter typhoid to this source, for he has shown that during cold weather oysters go into a condition of rest or hibernation, when the ciliary movement ceases and feeding does not occur, and the oysters become practically free from sewage organisms, even when lying in sewage-polluted beds. A bacteriological study of the oysters sold in Baltimore was undertaken, therefore, to determine whether they contain organisms derived from the intestinal tract and whether their content in bacteria varies with the season of the year.

Twelve different lots of oysters, with five in each lot, were examined. They were purchased in various shucking houses, where they were said to come from four different areas—Chesapeake and Lynnhaven bays and the York and Rappahannock rivers. This examination indicates the quality of oysters at the time they are sold, and not at the time of collection. The methods employed were those adopted by the Committee on

Standard Methods of Shell Fish Examinations of the American Public Health Association. When the oysters were collected at the shucking houses, certain oysters with deep bowls were purchased and carried to the laboratory, where five of the most suitable were selected for examination. The outside of the shell was first thoroughly washed with running water to free it from dirt and then allowed to dry in the air. It was then sterilized by exposure to the free flame, especially along the thin edge, after which the oyster was opened with a shucking knife, also sterilized in the free flame. The mother liquor or shell juice was immediately drawn off in sterile pipettes and dilutions of 1-10, 1-100 and 1-1000 made up with sterile water. From these dilutions dextrose fermentation tubes were planted to determine the presence of fermenting bacteria, intestinal in origin, and agar plates poured to determine the approximate number of bacteria in each oyster. Finally, those fermentation tubes, in which an active evolution of gas had taken place, were plated and characteristic colonies transferred to agar. Colonies were also transferred from the agar plates used for making the counts to agar and both sets of cultures identified by means of the ordinary culture media.

In determining the quality of the oysters examined the standard method already referred to was followed. By it the oysters are scored in the following manner: The presence of *Bacillus coli* or some other gas producer in each of the five

TABLE I.
BACTERIOLOGICAL SCORING OF BALTIMORE OYSTERS.*

Source and date.	Oyster.	Dilution 1-10.	Dilution 1-100.	Numerical value.	Agar count per cc.
Rappahannock River, Lot I, 10-29-'12.	1	0	0	0	2,833
	2	0	0	0	2,193
	3	0	0	0	547
	4	+	+	100	2,533
	5	0	9	0	1,033
				Score	100
Chesapeake Bay, Lot II, 11-2-'12.	1	+	+	100	63,866
	2	+	+	100	3,900
	3	+	+	100	75,666
	4	+	+	100	57,666
	5	+	+	100	23,333
				Score	500
York River, Lot III, 12-3-'12.	1	+	0	10	6,700
	2	+	+	100	20,133
	3	+	+	100	9,560
	4	+	+	100	24,466
	5	+	+	100	2,560
				Score	410
Rappahannock, Lot IV, 1-14-13.	1	+	0	10	No count.
	2	+	0	10	Do.
	3	0	0	0	Do.
	4	0	0	0	Do.
	5	0	0	0	Do.
				Score	20
York, Lot V, 1-20-'13.	1	0	0	0	12,000
	2	+	0	10	80,000
	3	0	0	0	12,000
	4	0	0	0	15,000
	5	0	0	0	39,000
				Score	10
Rappahannock, Lot VI, 1-28-'13.	1	0	0	0	No count.
	2	0	0	0	Do.
	3	0	0	0	Do.
	4	+	0	10	Do.
	5	0	0	0	Do.
				Score	10
Chesapeake, Lot VII, 2-3-'13.	1	0	0	0	2,000
	2	0	0	0	0
	3	+	0	10	No count.
	4	0	0	0	1,000
	5	0	0	0	1,000
				Score	10
Lynnhaven, Lot VIII, 2-6-'13.	1	+	+	100	No count.
	2	+	0	0	16,000
	3	+	0	0	25,000
	4	+	+	100	1,132,000
	5	0	0	0	0
				Score	200
Chesapeake, Lot IX, 2-11-'13.	1	+	0	10	No count.
	2	0	0	0	12,000
	3	0	0	0	No count.
	4	0	0	0	3,000
	5	0	0	0	0
				Score	10

*The names of the various lots of oysters employed in this table must not be taken too literally, since there is no proof that the oysters were actually collected in the various areas according to which they are labeled. Indeed there are some grounds for believing that the names are merely trade-names employed to indicate the size of the oysters and have no relation to their source of collection.

TABLE I—Continued.
BACTERIOLOGICAL SCORING OF BALTIMORE OYSTERS.*

Source and date.	Oyster.	Dilution 1-10.	Dilution 1-100.	Numerical value.	Agar count per cc.
Lynnhaven, Lot X, 2-18-'13.	1	+	0	10	3,000
	2	0	0	0	No count.
	3	+	0	10	1,000
	4	+	+	100	3,000
	5	+	+	100	1,000
				Score	220
Rappahannock, Lot XI, 4-1-'13.	1	+	+	100	14,000
	2	+	0	10	13,000
	3	0	0	0	1,000
	4	+	+	100	12,000
	5	+	+	100	11,000
				Score	310
Rappahannock, Lot XII, 4-16-'13.	1	+	+	100	13,000
	2	+	+	100	51,000
	3	+	+	100	16,000
	4	+	+	100	16,000
	5	+	+	100	8,000
				Score	500

*The names of the various lots of oysters employed in this table must not be taken too literally, since there is no proof that the oysters were actually collected in the various areas according to which they are labeled. Indeed there are some grounds for believing that the names are merely trade-names employed to indicate the size of the oysters and have no relation to their source of collection.

oysters in any lot is given a value which represents the reciprocal of the greatest dilution in which the gas test is positive. For example, if gas is present in a dilution of 1-10, the numerical value for the oyster is 10; if present in a dilution of 1-100 it is 100. The numerical values of the five oysters in each lot are added, in order to give a score to that oyster-bed for that particular time of the year. The tests upon which the score is based are only presumptive ones, but in most cases are confirmed by the cultural reactions of the organisms subsequently isolated. The various lots of oysters were scored according to this method and the scores are given in Table I. The agar counts for each oyster are also included.

A number of suggestive points are brought out in considering the results tabulated above. It may be noted first that the bacterial findings indicate that the oysters sold in Baltimore are in general free from sewage contamination. Thus six out of the twelve lots may be regarded as entirely satisfactory, having scores of 100 or less and showing less than three positive fermentation tests out of five in 0.1 cc. portions. Such lots of oysters would be regarded as free from pollution according to the standards of the Bureau of Chemistry of the United States Department of Agriculture and by the Rhode Island Shell Fish Commission, which bodies have adopted the most rigid regulations in America.³ Of the lots which would be condemned by these standards, two, Nos. XI and XII, from the Rappahannock River, were collected in April, the last month of the oyster season, at a time when the weather was quite warm. Of the four other lots whose score was such as to indicate sewage contamination, one, No. II, was collected early in November. This leaves only three lots of oysters in the entire number examined in cold weather which would be

condemned by the most rigid standard. When it is remembered that some time necessarily elapses between the time of collection and time of sale, during which period the micro-organisms in the oyster have an opportunity to multiply, these findings must be regarded as pretty favorable.

The most striking point brought out in this table is the distinct change in the character of the oysters, according to the time of the year. Thus in the early fall the scores were high, in the cold weather of midwinter low, and again high in the spring. This is indicated by striking an average for the various lots of oysters as is done in the following table:

TABLE II.
SEASONAL VARIATION OF BACTERIAL FINDINGS.

Source.	Average Fall Score.	Average Winter Score.	Average Spring Score.
Rappahannock	100	15	405
York	245	10	No exam.
Chesapeake	500	10	No exam.

Here it may be seen that during the cold winter months the scores of the three lots of oysters examined at different seasons are all low and the oysters free from contamination. These results confirm in a general way the opinion of Gorham and raise a serious question whether the typhoid fever which occurs in Baltimore during the cold months of winter can reasonably be attributed to oysters. Finally, it may be noted that there is a distinct correlation between the number of bacteria in each oyster and the number of gas producers as determined by the fermentation tube. A low bacterial count is associated with absence of fermentation, and a high count with a fermentation produced by considerable fractions of a cubic centimeter. This seems to indicate that the increase of bacteria which the various oysters show is in large part due to a multiplication of the intestinal organisms and not to an increase of the ordinary water species. This correlation between bacterial count and fermentation is indicated in Table III. It should be noted that no such correlation exists ordinarily in milk, as we have shown in a previous paper.*

VARIETIES OF MICROORGANISMS FOUND IN BALTIMORE.

Many of the oysters examined revealed the ordinary spore-bearing and pigmented bacteria which are characteristic of water and have no significance in this connection. In addition a number of non-spore-forming, non-pigmented species were isolated from time to time. These organisms were worked over with care and their cultural peculiarities established on the usual media. In some instances their identification presented no difficulties. Thus *Bacillus coli* was obtained 14 times in 17 oysters with positive fermentation tests. It had the classical reactions of motility and decolorization by Gram's stain, acidifying and coagulating milk, failing to liquefy gelatin, producing indol, and fermenting the carbohydrates with the evolution of a gas consisting of a mixture of hydrogen and carbon dioxide, with an excess of the former. Organisms differing from *Bacillus coli* by their gas formula, producing an excess of carbon dioxide over hydrogen and thus corresponding

to *Bacillus cloacæ* of Jordan, were obtained five times. They differed from Jordan's *Bacillus cloacæ* in not liquefying gelatin, but should probably be included in this group.⁵ Their acidification and coagulation of milk was also much slower than that of *Bacillus coli*. *Bacillus alkaligenes* of Petruschky was isolated from one oyster. This organism also presents no difficulties in its recognition, since its alkaline reaction in

TABLE III.
CORRELATION BETWEEN FERMENTATION AND BACTERIAL COUNT.

Lot No.	Sample No.	Bacterial count.	Dextrose dilution 1-10.	Fermentation 1-100.
I.....	1	*2,833	0	0
	2	2,193	0	0
	3	547	0	0
	4	2,533	+	+
	5	1,033	0	0
II.....	1	63,866	+	+
	2	3,900	+	+
	3	75,666	+	+
	4	57,666	+	+
	5	23,333	+	+
III.....	1	*6,700	+	0
	2	20,133	+	+
	3	9,560	+	+
	4	24,466	+	+
	5	2,560	+	+
V.....	1	12,000	0	0
	2	80,000	+	0
	3	12,000	0	0
	4	15,000	0	0
	5	39,000	0	0
VIII.....	2	16,000	+	0
	3	25,000	+	0
	4	1,132,000	+	+
	5	0	0	0
X.....	1	3,000	+	0
	3	1,000	+	0
	4	3,000	+	0
	5	1,000	0	0
XI.....	1	14,000	+	+
	2	13,000	+	0
	3	1,000	0	0
	4	12,000	+	+
	5	11,000	+	+
XII.....	1	13,000	+	+
	2	*51,000	+	0
	3	16,000	+	+
	4	16,000	+	+
	5	8,000	+	+

*Indicates where gas should have appeared in one or both dilutions, but failed. These exceptions only number 3 out of 38 samples tabulated, approximately 8%.

milk and its failure to liquefy gelatin or to act upon any of the carbohydrates place it quite definitely. In addition to these well-defined species, a number of forms were encountered which presented some difficulty in classification. The most frequent of these was an organism with some of the reactions of *Bacillus coli* and others of *Bacillus cloacæ*. Thus it splits up the carbohydrates in the same manner as *Bacillus coli*, with a gas preponderating in hydrogen over carbon dioxide, and acidifies and coagulates milk with great rapidity. It thus resembles *Bacillus coli*. At the same time it causes a rapid liquefaction of gelatin in a funnel-shaped growth along the

line of inoculation, resembling *Bacillus cloacæ*. This organism is identical with the organism isolated by Ford and Watson⁶ from the Baltimore city water and described by them as a liquefying fermenter. It was isolated five times in our work and was a well-defined species. In addition, we found on various occasions bacteria which agreed in their cultural reactions with some of the rarer intestinal species originally described by Ford⁷ from the intestinal tract. The most important of these were: *Bacterium oxygens*, an organism acidifying and coagulating milk, producing no liquefaction of gelatin and growing only in the open bulb of the fermentation tube; *Bacillus oxyphilus*, acidifying and coagulating milk, not liquefying gelatin and producing acid from dextrose growing in the closed arm of the fermentation tube; two species identified as *Bacillus chymogenes* and as *Bacillus chylogenes*, acidifying and coagulating milk, liquefying gelatin and producing acid from dextrose, with growth in the closed arm in one case, but without it in the other. While these organisms were found on but a few occasions, their cultural reactions were quite distinct and the species were well marked. Whether they have

any significance in oysters cannot be decided at the present time. Species like *Bacillus coli* and *Bacillus cloacæ*, however, and probably the liquefying fermenter of Ford and Watson, are surely indicative of sewage pollution of the oysters from which they are isolated. This is further borne out by the fact that these organisms were isolated from those lots of oysters which would be condemned by the methods of scoring described above. In this connection, it should be noted that on no occasion were organisms of the type of *Bacillus typhosus* or *Bacillus paratyphosus* encountered.

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BRIEF NOTE ON THE BALTIMORE CITY WATER.

By MARJORIE DIETZ.

(From the Laboratory of Hygiene and Bacteriology, The Johns Hopkins University.)

In a recent paper by Ford and Watson^{*} it was pointed out that the chemical treatment of the Gunpowder water, the main source of the Baltimore City supply, had not resulted in as great a diminution of intestinal bacteria as was to be expected from the experience of other cities. The number of bacteria in the water was markedly diminished, but the fermenting organisms continued to appear with some frequency. On January 1 a different method of applying the chemical treatment was adopted, alum being added first, followed by the hypochlorite of sodium. This treatment of the water was applied at the Montebello reservoirs instead of at Loch Raven. It seemed of interest, therefore, to make a further study of the city water to determine whether this change in the method of applying the chemical treatment had resulted in any change in the character of the water. Our examinations were carried out over a period of three months and gave results which were entirely different from any heretofore obtained in this laboratory. During this time the bacterial count has been surprisingly low, averaging only fifteen colonies to the cubic centimeter. On several occasions only six or seven colonies were to be found in the plates and on no occasion has there been a count of more than twenty bacteria per cubic centimeter. The type of bacteria has completely changed, moreover, only the spore-bearing organism characteristic of the after-growths seen in chemically treated water being found. The conclusions to be drawn from the agar plates were confirmed by the fer-

mentation tubes, which were uniformly negative for fermenting organisms in one cubic centimeter quantities and usually negative in five and ten cubic centimeters. On three occasions active fermentation occurred with ten cubic centimeters and on two occasions with five. Plates poured from these fermentation tubes revealed no aerobic colonies of the intestinal type, only the ordinary spore-bearers. The suspicion arose, therefore, that the fermentation in these tubes was not due to ordinary intestinal fermenters, but to some spore-bearing anaerobe, possibly the *Bacillus aerogenes capsulatus* or "gas bacillus" of Welch and Nuttall. This suspicion was confirmed by the inoculation of a rabbit with material from one of these tubes. The rabbit was killed and its body placed in a warm room for twenty-four hours. After the lapse of this time characteristic gas oedema was present throughout and the organism was obtained in pure culture from the blood.

As a result of our examination of the city water, it can be stated that the change in the method of applying the chemical treatment has resulted in a marked change in the character of the water, the intestinal bacteria disappearing almost entirely. The city thus is in a position to purify its water supply by chemical treatment and eliminate its water-borne typhoid fever. Such a practice is to be recommended on all public health grounds, but on no account should the chemical treatment be regarded as a substitute for sand filtration. It should serve only as an emergency procedure till the system of sand filters is installed and put in complete operation.

^{*} Ford and Watson: Johns Hopkins Hosp. Bull., 1913, XXIV, 226.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

October 1, 1913.

Two Cases of Helminthiasis (from the Out-Patient Department of the Johns Hopkins Hospital). DR. DAVID I. MACHT, Instructor in Medicine, The Johns Hopkins University.

The following two cases which I had occasion to study at the Johns Hopkins Dispensary last summer are sufficiently exceptional to deserve reporting.

CASE No. F. 8193.—J. W., male, white, married, age 25 years, American, farmer. Was admitted to the Dispensary June 19, complaining of "indigestion, pains in the stomach, and vomiting of worms."

Family History.—Negative.

Past History.—Negative. Bowels have been regular prior to the present illness.

Present Illness.—Has been suffering for the past four years from indigestion, which takes usually the form of irregular pains more or less severe, of variable duration, coming on especially after eating. His bowels are irregular, usually constipated, necessitating the use of Epsom salts. Appetite, however, has always remained good. Has lost 15 lbs. in weight, in the last three months. For the last four weeks appetite has been ravenous. "The more I eat, the more I want," as he says. In spite of the good appetite he has lost weight, been nauseated, and vomited a number of times in the latter part of the day.

Three weeks ago, after severe retching, he vomited a worm, which he described as having the appearance of a fish worm. He never noticed any worms in the stools before that time, but has since. Feels weak, and complains of pains around the waist line.

Physical Examination.—Looks thin, pale, and feverish. Tongue heavily coated; foul odor from the mouth.

Temperature 100.5° F. Pulse, 120 to the minute, regular, of moderate volume and tension.

Heart and Chest.—Negative.

Abdomen.—Flat and symmetrical. No tenderness on pressure, no masses felt. Liver and spleen not enlarged. Stomach is distended by gas and rises high in the left axilla.

Urine contained no albumin or sugar.

Diagnosis.—From the history of the case, a provisional diagnosis of ascaris infection was made.

The patient was given 1 gr. doses of santonin, and two days later brought some ten or twelve full-size specimens of ascaris lumbricoides which he had passed, thus confirming the diagnosis.

CASE No. F. 5242.—R. K., female, white, married, age 21 years, was admitted to the Dispensary on May 19, 1913. Her complaint was "tapeworms."

Family and Past History.—Negative.

Present Illness.—In December, while in the early months of pregnancy, patient was vomiting frequently. One day after a violent retching she vomited a portion of a tapeworm. Becoming terribly frightened she called to her mother who ran to her assistance and pulled the worm out of the patient's mouth. The segment thus expelled was about one and a half yards long. Following the shock of fright, the patient had a miscarriage. Two days later she passed two long pieces of worm per rectum, and has since then for half a year been passing small segments in the stools.

At present patient complains chiefly of weakness and nervousness. She sleeps well and has no pains. Appetite is not very good; bowels are irregular. No spasms or convulsions. No more vomiting.

Urine.—No albumin and no sugar.

Diagnosis.—From the history of the case a provisional diagnosis of tapeworm was made. This was confirmed by the therapeutic test. The patient was given two ½ drachm doses of oleoresini aspidii and two days later brought a jar full of tapeworms. On examination of the segments it was found to be a *tænia saginata*. The head could not be found.

The above two cases are remarkable for the vomiting or expulsion of intestinal parasites by mouth, complained of in both, which we may term "Helminthiasis." Vomiting of worms is not unknown, and yet is considered a rare occurrence. The commonest cases on record are those of ascaris lumbricoides. This *nematode* may wander into various organs of the body and cases are reported of its getting into the mouth, the nose, the larynx (causing fatal suffocation) and even the Eustachian tube. (Eulenburg: Real Encyklopädie der Gesamten Heilkunde, 1896, X, 269, etc.)

Vomiting of tapeworms or their segments, however, is a very much rarer occurrence, and only very few such cases have been reported. Only five instances have been collected in the great work on Animal Parasites by Davaine. (Traité des Entozoaires. Paris, 2d ed.) Mosler and Peiper (Nothnagel's Handbuch, 1897, VI, 58) write: *nur äusserst selten ist der Abgang von Proglottiden beim Erbrechen gesehen worden*. My second case undoubtedly belongs to this class. That abortion should have been induced by the shock is not at all surprising, and recalls one of the cases quoted by the above writer, where a peasant was seized with a vomiting spell, and expelled part of a worm by mouth. A physician tried to pull out the rest, but the poor fellow, frightened, thought that his bowels were being drawn out and would not allow it.

In this connection I have analyzed all the cases of tapeworm and ascaris infection admitted to the Johns Hopkins Dispensary in the last eight years.

I have found in all 65 cases of *tænia* infection, and nine cases of infection with ascaris lumbricoides. Of the 65 *tænia* cases, 42 were diagnosed as *tænia saginata*, one was bothryocephalus latus, and in the remaining cases the species was not stated. It was interesting to note that the majority of tapeworm cases (42 out of 65) were in women, and the ages of the patients were almost all below 40 years. Vomiting as a symptom is noted only in five out of the 65 cases, or 7%, a figure rather less than that given by Stiles (Osler's Modern Medicine I, 560). Of the ascaris cases there was only one case out of the nine that gave a history of vomiting, and all of these cases with the exception of one were in children, unlike the one I described, which occurred in an adult.

Physiology
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THE COLLOIDAL GOLD REACTION IN THE CEREBROSPINAL FLUID.*

By SYDNEY R. MILLER, M. D., and ROBERT L. LEVY, M. D.

(From the Laboratory of Internal Medicine, The Henry Phipps Psychiatric Clinic, and the Medical Clinic of The Johns Hopkins Hospital.)

1. INTRODUCTION.

The examination of the cerebro-spinal fluid is essential in the study of many neurological and psychiatric conditions. From it much information of diagnostic and prognostic importance is obtained, while recent studies, notably by Swift and Ellis,¹ indicate that it is a valuable index of the efficacy of treatment, particularly the specific therapy of syphilitic diseases of the central nervous system. Much doubt still exists as to the exact nature, origin and composition of spinal fluid, though the investigations of Dandy and Blackfan,² Dixon and Halliburton³ and others promise much for the final answer to these problems. Particularly is opinion divided over the form and combinations of proteins which occur in normal and abnormal fluids. Physical-chemical methods thus far have failed to yield results of more than theoretical value and the same may be said of pure chemistry. The occurrence of ferments, investigated by Kafka⁴ and Szabó,⁵ while of interest, is yet of doubtful clinical value, and Abderhalden's⁶ sero-diagnostic method is still in a somewhat experimental and empirical state, quite apart from the fact that its performance is attended with many difficulties and numerous possible

sources of error. There are many obstacles in the way of spinal fluid analysis, notably the fact that its withdrawal, even in small amounts, from normal individuals is not infrequently followed by unpleasant symptoms. The introduction therefore of a method of study which requires minimal amounts of fluid is greatly to be desired, since only by an exact acquaintance with the normal can we hope to appreciate deviations from it.

There are three findings in the spinal fluid of recognized diagnostic value; first, a positive Wassermann reaction; second, an increased cell count, and third, an increased protein content, commonly referred to in the literature as the Phase 1 of Nonne. The Wassermann reaction, negative in nearly all fluids examined during the first three stages of syphilis, becomes increasingly positive when applied to cases of cerebro-spinal lucas, tabes and paresis, averaging between 90% and 100% positive in the last condition. Opinion is still somewhat divided as to the best method of investigation of the cellular elements, most workers being content with a simple quantitative estimation of their increase, while others, as Alzheimer⁷ and Szécsi,⁸ rely more upon qualitative changes as revealed by histological and staining methods. Nonne's⁹ Phase I, modified by numerous workers, notably Ross and Jones¹⁰ and Noguchi,¹¹ represents nothing more than a pro-

*Read before the Johns Hopkins Hospital Medical Society, March 2, 1914.

tein-complex group reaction, though it is commonly accepted, when positive, as indicating an increase in the globulin content of the fluid. That globulins in abnormal fluids constitute only a part of the precipitate caused by one-half saturation with ammonium sulphate can readily be demonstrated. Although positive in from 95% to 100% of luetic infections of the central nervous system, Phase I alone does not enable one to differentiate between luetic and non-luetic conditions. It is incorrectly stated that the intensity of the reaction is always greater in the specific infections. While these three tests meet most of the requirements of clinical diagnosis, they tell us nothing concerning the factors responsible for their causation.

The present report deals with one of the recent tests applied to the spinal fluid, in which colloidal chemistry plays the leading rôle. In view of the wide range to which the relatively new subject of colloidal chemistry is applied, and the exactness of the laws which control and determine colloidal reactions, and their extreme delicacy, it is not surprising that this science should have found a place in clinical laboratory methods. If the predictions of such investigators as Ostwald are to be relied upon, we may ultimately expect to learn most concerning the aggregation of living protoplasm, the laws which govern immunity, the basis for the Wassermann reaction, etc., by the use of colloidal chemistry and allied sciences.

The foundation for the present test was laid by Zsigmondy¹² in 1901. Having worked exhaustively with solutions of colloidal gold, he attempted with success to use it as a means for the quantitative estimation of protein substances. It was well known that colloidal solutions of gold or other metals are precipitated or "coagulated out" by electrolytes, this coagulation depending upon the degree of concentration as well as the valency of the electrolytes employed. It was also recognized that colloids are electrically charged and that two oppositely charged colloids mutually precipitate one another, though only in definite quantitative amounts. If these amounts are exceeded in one way or the other, no precipitation occurs. Zsigmondy discovered that solutions of proteins give protection to colloidal solutions of gold up to a certain point, and he determined the so-called *Goldzahl* for various protein substances, by which is meant the number of milligrams of the protein employed, just sufficient to prevent the precipitation of 10 cc. of colloidal gold of a percentage of .0053 in the presence of 1 cc. of 10% NaCl solution. By this method it can be determined whether a given protein is absolutely pure, or granted this is the case, how much is present in a given solution. In attempting to apply this gold protection method to the study of the proteins of the spinal fluid, Lange,¹³ in 1912, discovered that instead of securing protection, quite the reverse occurred, particularly in conditions in which the spinal fluid contained an abnormal amount of protein substance, notably in the syphilitic diseases of the central nervous system. Moreover, he observed that the reaction which occurred took place within certain dilution limits which seemed to be more or less specific, thus making possible, by means of colloidal solutions of gold, the differentiation between syphilitic and non-syphilitic conditions. Since that time, the test as used by

various observers has yielded fairly consistent results, which will be discussed in more detail in another portion of the present report.

2. APPARATUS AND SOLUTIONS REQUIRED.

A. GLASSWARE.

For the preparation of all reagents required, the following Jena glassware is necessary:

1. Flasks: 1000 cc., plain and distilling, the latter provided with side glass outlet tube.
2. Certified graduates: 25 and 1000 cc.
3. Beakers: 1 and 2 litre sizes.
4. Liebig condensers: all glass.
5. Glass stoppered stock solution bottles, 2 litres. With the exception of the condensers, all glassware is rinsed with strong HCl, followed by distilled water and hot air sterilization for 30 minutes. Condensers are cleaned with steam and rinsed by the first 200 cc. of the distillate, which is subsequently thrown away.

In the actual performance of the test there are needed:

1. Test tubes: 120x12 mm., thick walled.
2. Certified pipettes: 1, 10, 25 cc.

The tubes are cleaned each time by boiling in 10% potassium bichromate solution, and then in distilled water, using a brush when necessary, to remove all traces of precipitated gold from the sides and bottom. After sterilization they should be kept in a suitable dust-proof glass container until used. It is important to avoid contamination of the tubes by alkaline cleaning mixtures. Pipettes, rinsed in an automatic washer, are dried with alcohol and ether and sterilized in a pipette box. Confusing results will be avoided if a suitable supply of glassware is reserved solely for use in the test. *We are convinced that upon the care with which the cleaning and sterilization of glassware is carried out depends the success of the preparation of the gold solution and the reliability of the entire reaction.*

B. SOLUTIONS REQUIRED.

(1) *Distilled Water*.—The preparation of the distilled water is the most important stage in the making of colloidal gold solutions. Ordinary tap water and ordinary distilled water are both unsuited for preparing the reagent. Freshly distilled water, received in a sterile flask provided with a side glass connecting tube, is immediately redistilled and used within two or three hours; if allowed to stand much longer the water seems to acquire properties which render it unfit for use. No rubber stoppers or connections should be used in the distilling apparatus.

(2) *NaCl Solution (0.4%)*.—This solution, made with doubly distilled water and Merck's "Blue Label" sodium chloride, keeps for a long time, but it is desirable to prepare it at least every two weeks. There seems to be no advantage in making this dilution each time from a stock 10% solution, as recommended by some authors. This particular strength is used because it causes no coagulation of colloidal gold. At the same time it is of sufficient concentration to hold globulins and nucleo-proteins in solution. Spinal fluids diluted with water exert no action upon a gold solution.

(3) *Colloidal Gold Solution*.—The ingredients required to prepare this indicator are:

- | | |
|-------------------------------------|-------------------------------------|
| a. Doubly distilled water. | |
| b. Gold chloride crystals (yellow). | } Merck's "Blue
Label" Reagents. |
| c. Potassium carbonate. | |
| d. Formalin. | |

One litre of water is heated to 60° C. in a sterile Jena beaker. At this temperature 10 cc. each of a 1% aqueous solution of gold chloride and a 2% solution of potassium carbonate are added synchronously and thoroughly mixed at once. From this point the solution is heated as rapidly as possible, by using a four or

six flame Bunsen burner, until a temperature of about 90°C., but not exceeding 95° C., is reached. The flame is turned out, and while the contents of the beaker are briskly agitated, 10 cc. of a 1% aqueous solution of formalin are gradually added. The previously clear, colorless liquid at once undergoes a brilliant reaction, with reduction of the gold to a colloidal state, shown by the production of a beautiful play of colors. The resultant solution should meet the following criteria:

1. Color: A rich brilliant red with an orange glint when viewed in thin layers. The presence of any purple or blue shades must be avoided.
2. Such solutions must be absolutely clear and transparent when seen from any angle by any light. The existence of a superficial fluorescent layer is an indication for rejecting the reagent.
3. Boiling causes no change in the physical properties or reacting ability of good solutions.
4. They do not dialyse or diffuse.
5. Protected from evaporation, such solutions remain unchanged for an indefinite length of time, exposed to light and room temperature.
6. With normal spinal fluids, such solutions give no reaction, while with a paretic fluid complete *Ausflockung* occurs in the first 4 to 6 tubes.

Other methods for the standarization of gold solutions are greatly to be desired so that workers may always employ a comparable indicator. Occasionally, a solution meeting all of the first five requirements, will fail absolutely to react with a known abnormal spinal fluid: the cause for this is not known to us. We have tried other reducing agents, such as glucose and tannin, but with results inconsistent and generally unsatisfactory. It is useless to attempt to "doctor up" a solution which falls short of the first two requirements. Provided due care is exercised in the preparation of the water and the cleaning of the glassware, satisfactory colloidal solutions can always be obtained by the method above described.

C. THE CEREBROSPINAL FLUID.

The lumbar puncture needles employed, preferably made of iridio-platinum, should not be boiled prior to use. They should be cleaned by drawing through them distilled water, alcohol and ether, after which they are sterilized in an ignition tube along with two small test tubes cleaned with the same reagents, as shown in Fig. 1. Every needle must be examined frequently and all traces of rust removed from its interior and stilette. If the pressure of the spinal fluid is to be determined, it must be done first, and after disconnecting the manometer, 10 or 15 drops of fluid are allowed to escape before any is collected for use. Fluids can be kept for at least several days before the test is carried out, though we have examined all specimens as soon as possible. Spinal fluids contaminated either with blood or bacteria are unfit for examination. Sterile fluids kept on ice for several weeks show practically no change in their reaction to solutions of colloidal gold.



FIG. 1.
Sterile
Lumbar
Puncture
Outfit.

3. TECHNIQUE OF THE TEST.

Place 11 sterile test tubes in a suitable rack. With a 10 cc. pipette measure 1.8 cc. of 0.4% salt solution into the first tube, and 1 cc. into each of the remaining. By means of a graduated 1 cc. pipette 0.2 cc. of spinal fluid are now added to the first tube and thoroughly mixed: it is to be noted that unless the contents of the pipette are completely expelled each time, an error in the dilution is introduced. Transfer 1 cc. of the 1-10 dilution of spinal fluid from the first to the second

tube, where the mixing process is repeated and a 1-20 dilution results. In a similar manner dilutions are made in the remaining eight tubes, 10 dilutions in all, ranging from 1-10 to 1-5120. The 11th tube serves as a control to which no spinal fluid is added. It does not seem necessary to carry the dilutions higher, though in some isolated cases the reaction obviously would have gone beyond the 10th tube. After this dilution has been completed, 5 cc. of colloidal gold are added to each of the 11 tubes with a 25 cc. certified pipette. The reagent should be added and mixed as rapidly as possible; otherwise, reactions which are misleading and inaccurate will occur. The length of time required thus to examine a spinal fluid is approximately 5 minutes. While it is true that after some experience one may judge at once, with fair accuracy, of the degree of the reaction, it is best to wait 10 to 12 hours before making final readings. It has been our custom, therefore, to carry out the test late in the afternoon, reading the results the following morning, the tubes meanwhile standing at room temperature, and not necessarily stoppered. Reactions remain unchanged for at least 2 to 3 weeks, provided evaporation is guarded against and the tubes are kept in the ice-box. No attempt to record final readings with artificial light should be made, since this renders true color values extremely difficult to interpret.

4. THE REACTION OBSERVED.

This consists in color changes due to alterations in the dispersion value of the colloidal gold. A negative reaction may be represented by zero; the maximum precipitation, obtained with paretic fluids, consisting in complete decolorization, may be expressed conveniently by the figure 5. Between these two extremes, shades occur, running from pale blue through purple, violet, lilac and red-blue, to which numerical values have been assigned, as shown in Fig. 2. This diagram also indicates a method for the

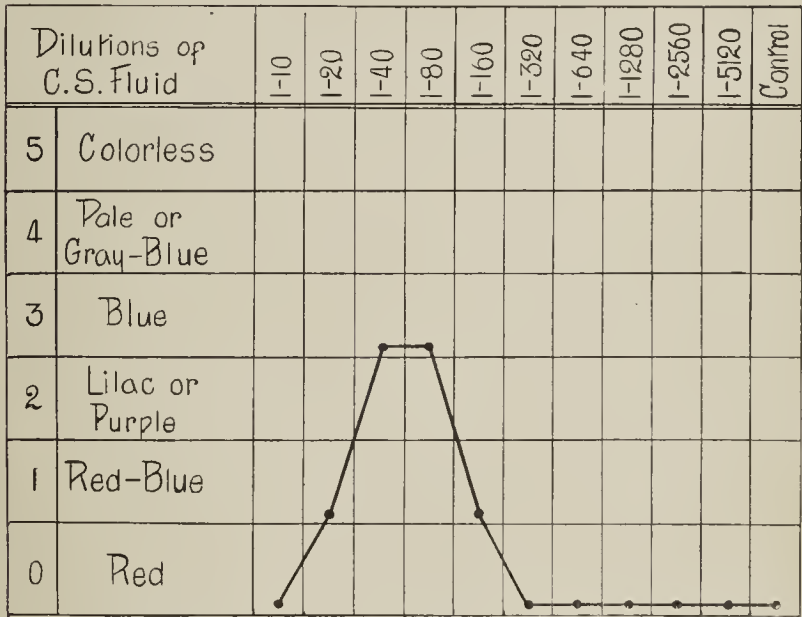


FIG. 2.—Diagram showing numerical values assigned to colors, and a reaction in the "luetie zone."

graphic representation of reactions. The regularity with which these color changes occur at certain maxima is quite striking. For this reason certain so-called characteristic reaction zones have been described. These are:

1. The "luetie zone" confined to the first 4 or 5 tubes. In this the precipitation is usually greatest in the dilutions 1-40 to 1-160 and never exceeds a "4" reaction.
2. The "meningitic zone" with *Verschiebung nach oben*, a phrase introduced by Lange. By this is meant a reaction maximum in the higher dilutions. Such a curve is represented in Fig. 3.

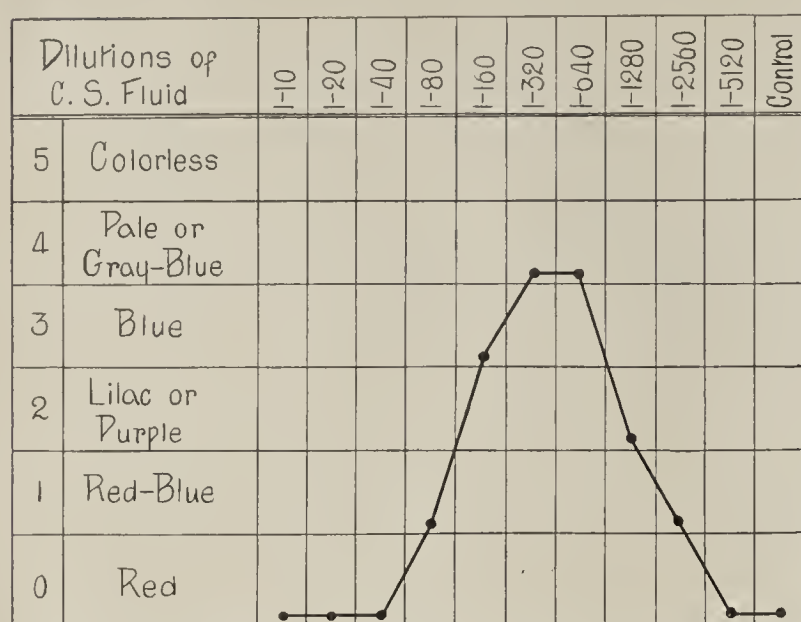


FIG. 3.—The reaction in meningitis with typical *Verschiebung nach oben*.

3. From observations herewith presented we feel that the curve in dementia paralytica is sufficiently constant to justify the introduction of the term "paretic zone." This zone comprises the first 3 to 6 tubes, in which the reaction is characteristically of the "5" type (Fig. 4).

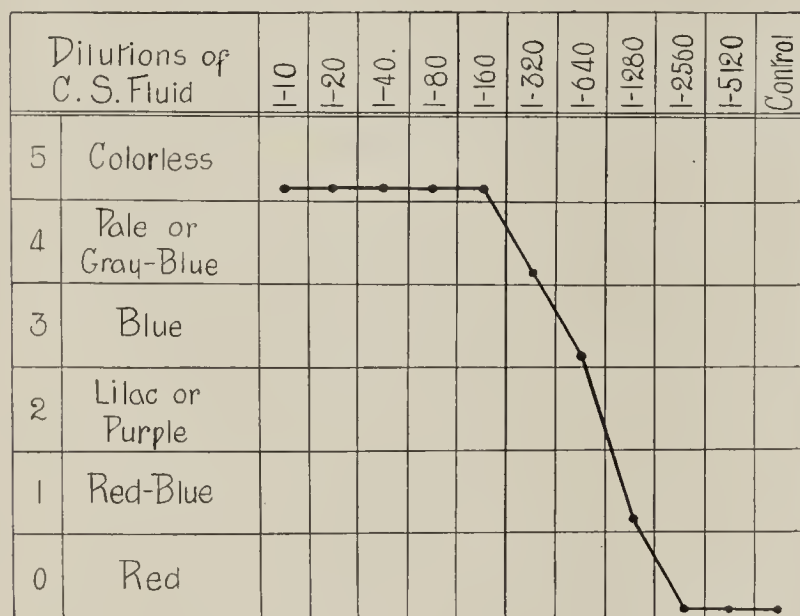


FIG. 4.—The characteristic curve of general paresis.

5. NATURE OF THE REACTION.

The exact nature of the reaction, it must be admitted, is not known. This is necessarily the case, since the exact combination and nature of the protein substances which may occur in the spinal fluid under normal or abnormal conditions, have not been determined. Lange is inclined to interpret the reaction as an indication of the occurrence of different qualitative mixtures of protein substances rather than of a true quantitative increase in one or other of the protein constituents. There is considerable evidence in favor of this view, since the strength of the reaction apparently bears no constant relation to the amount of protein present, as revealed by the ordinary tests. Other writers, as Zalosiecki,¹⁴ are inclined to view it as an immunity reaction, more or less analogous to

the "floccule reaction" of Porges and Meier,¹⁵ Hermann and Perutz¹⁶ and others, used as a diagnostic test for luetic conditions. Exponents of colloidal chemistry rather incline to the idea that the color changes are induced by variations in the dispersion value of one or more colloidal substances present in the spinal fluid. No attempt has been made by us to prove which, if any, of these theories is correct, but merely to determine whether or not the test is of sufficient value to warrant its adoption as an aid to clinical diagnosis.

6. ROUTINE FOLLOWED.

The present report is based upon the examination of 210 spinal fluids secured from 171 cases.*

All fluids have been subjected to the following routine examination: *First*, a quantitative estimation of the cells has been made as soon after withdrawal of the fluid as possible, usually within ten or fifteen minutes. We have used a diluting solution consisting of distilled water, 50 cc.; glacial acetic acid, 2 cc.; and methyl violet, 0.1 of a gram. This stains the nuclei of the cells with sufficient clearness to permit of a fairly accurate differential count at the same time that the quantitative estimation is made. In all instances counts have been made with the Fuchs-Rosenthal counting chamber. *Second*, increase in the protein content has been tested for by the Ross-Jones method. In our experience this test has yielded results which are both trustworthy and easily obtained. *Third*, the Wassermann reaction has been carried out by one of us on all spinal fluids and on specimens of blood from the same patients when available. Every fluid and serum has been tested with at least two, and in many instances with three, antigens, namely, a plain alcoholic extract of the human heart, a similar extract, strengthened by the addition of .4% cholesterol, and an alcoholic extract of syphilitic liver. It should be noted in passing, that in the great majority of the cases the results obtained with these three antigens have been parallel. There have been, however, undoubted cases of syphilitic infection in which the cholesterolized antigen alone has given a positive result, the other two antigens yielding an absolutely negative or, at most, a 1 + inhibition. Such cases are indicated in the reports given below. *Fourth*, the colloidal gold reaction.

7. TABULATION OF RESULTS.

Detailed case reports are herewith presented. The numbers 1-10 under Gold Reaction refer to the dilutions previously described. A star indicates that the fluid was sent from an outside source. Wassermann reactions positive with a cholesterol antigen only are indicated by the letter C. A cell count of ten or over has been regarded as a pleocytosis.

* The rapidity with which we have been able to secure this number of observations is due in large part to the hearty co-operation received from the various members of the medical, pediatric and dispensary staffs of this hospital, to whom we express our greatest appreciation. It is also a pleasure to acknowledge the receipt of numerous spinal fluids from the Manhattan State Hospital, through the kindness of Dr. Cheney; from the Central Islip Hospital, Long Island, through Dr. Wescott's help; and from the City Detention Hospital at Bay View, through the co-operation of Dr. Kenneth B. Jones.

TABLE I. MISCELLANEOUS GROUP.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
A. (2)...	Not done.	Negative.	1	Negative.	0	0	0	0	0	0	0	0	0	0	Pneumonia; meningismus.
B.B. (3)...	Negative.	do.	1	do.	0	0	0	0	0	0	0	0	0	0	Multiple sclerosis.
N.B. (4)...	do.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Hysteria; epileptiform attacks.
Do. (6)...	do.	do.	10	do.	0	0	0	0	0	0	0	0	0	0	Epileptiform attacks.
Di. (6)...	do.	do.	27	do.	0	0	0	0	0	0	0	0	0	0	Acute mania.
B. (8)...	do.	Not done.	1	do.	2	3	3	2	1	0	0	0	0	0	Brain tumor.
B. (9)...	do.	Negative.	800	Positive.	4	4	5	5	5	5	5	2	1	0	Cells mixed type.
			1184	do.	5	5	5	5	5	5	4	3	2		
			210	do.	5	5	5	5	4	2	1	0			Brain abscess.
B. (10)...	do.	do.	1	Negative.	0	0	0	0	0	0	0	0	0	0	Neurasthenia.
C. (11)...	do.	do.	1	do.	0	0	0	0	0	0	0	0	0	0	Migraine.
C. (13)...	do.	do.	0	do.	0	0	0	0	0	0	0	0	0	0	Manic depressive psychosis.
C. (19)...	do.	C. Positive.	2	Faintly +	0	0	0	0	0	0	0	0	0	0	Chronic nephritis; uraemia.
D. (24)...	do.	Negative.	6	Faintly +	0	0	0	0	0	0	0	0	0	0	Anxiety neurosis.
D. (130)...	do.	do.	2	Negative.	0	0	0	0	0	0	0	0	0	0	Dermatitis herpetiformis.
D. (25)...	do.	do.	5	do.	1	2	3	3	1	0	0	0	0	0	Typhoid fever; patient extremely toxic.
F. (129)...	Not done.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Oxycephaly.
F. (135)...	Negative.	do.	4	do.	0	0	0	0	0	0	0	0	0	0	Septicaemia.
G. (35)...	do.	do.	1	do.	0	0	0	0	0	0	0	0	0	0	Varicella.
H. (43)...	Not done.	do.	34	Positive.	0	0	0	0	0	0	0	0	0	0	Alimentary intoxication.
II. (46)...	Negative.	do.	4	Faintly positive.	1	1	1	2	3	2	0	0	0	0	Manic-depressive insanity.
J. (51)...	do.	do.	2	Negative.	0	0	0	0	0	0	0	0	0	0	Chronic encephalitis; operation.
J. (52)...	do.	do.	5	do.	0	1	1	2	1	0	0	0	0	0	Tumor of spinal cord; compression.
J. (53)...	do.	do.	2	Positive.	1	1	2	2	2	0	0	0	0	0	Psychoneurosis (?).
K. (59)...	do.	do.	9	Negative.	0	0	0	0	0	0	0	0	0	0	Acidosis; autopsy.
K. (156)...	do.	do.	4	do.	0	0	0	0	0	0	0	0	0	0	Copaiba rash.
K. (62)...	do.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Psychoneurosis.
L. (63)...	do.	do.	4	do.	0	0	0	0	0	0	0	0	0	0	Serous meningitis.
L. (64)...	do.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Psoriasis.
L. (66)...	Not done.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Eczema.
L. (68)...	Negative.	do.	5	do.	1	2	2	1	0	0	0	0	0	0	Positive history of lues. Cerebral sclerosis; convulsions.
M. (71)...	do.	do.	3	do.	0	0	0	0	0	0	0	0	0	0	Aenitis.
M. (72)...	do.	do.	2	do.	0	1	2	3	1	0	0	0	0	0	Dementia praecox; luetic history.
M. (73)...	do.	do.	4	do.	0	0	0	0	0	0	0	0	0	0	Pulm. tuberculosis.
M. (74)...	do.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Psychoneurosis.
M. (76)...	do.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Chronic nephritis.
M. (77)...	do.	do.	6	do.	0	0	0	0	0	0	0	0	0	0	Pneumonia; meningismus.
M. (78)...	do.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Psychoneurosis.
M. (79)...	do.	C. Positive.	3	do.	1	1	2	3	2	1	0	0	0	0	Cerebellar tumor (?).
M. (80)...	do.	Negative.	5	do.	0	0	0	0	0	0	0	0	0	0	Hydrocephalus.
M. (81)...	do.	C. Positive.	17	Positive.	1	1	2	2	1	0	0	0	0	0	Lead encephalopathy.
N. (84)...	do.	Negative.	0	Negative.	0	0	0	0	0	0	0	0	0	0	Syphilophobia.
P. (133)...	do.	do.	3	do.	0	0	0	0	0	0	0	0	0	0	Hysteria.
P. (88)...	do.	do.	3	do.	0	0	0	0	0	0	0	0	0	0	Psoriasis.
R. (92)...	do.	do.	5	do.	0	0	2	3	1	0	0	0	0	0	Cystic glioma; luetic history.
R. (93)...	do.	do.	12	do.	0	0	0	0	0	0	0	0	0	0	Neurasthenia.
R. (95)...	do.	do.	1	do.	1	2	2	1	0	0	0	0	0	0	Psychoneurosis. Tabes (?).
R. (97)...	do.	do.	8	do.	0	0	0	0	0	0	0	0	0	0	Chronic meningitis (?).
S. (131)...	do.	do.	9	do.	0	0	0	0	0	0	0	0	0	0	Cerebral sclerosis.

TABLE I. MISCELLANEOUS GROUP.—Continued.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
S. (105)...	Negative.	Negative.	9	Positive.	1	1	1	1	2	3	3	1	1	0	Cerebral sclerosis. Xanthochromia.
S. (134)...	do.	do.	3	do.	0	0	0	0	0	0	0	0	0	0	Compression of spinal cord.
S. (106)...	Not done.	do.	2	Negative.	0	0	0	0	0	0	0	0	0	0	Malnutrition.
S. (157)...	Negative.	do.	0	do.	0	0	0	0	0	0	0	0	0	0	Cerebral arterio-sclerosis.
S. (108)...	do.	do.	3	do.	3	3	2	2	2	1	0	0	0	0	Septicaemia; fluid contains bile.
T. (110)...	do.	do.	2	do.	0	0	0	0	0	0	0	0	0	0	Normal child.
T. (150)...	do.	do.	1	do.	0	0	0	0	0	0	0	0	0	0	Chronic nephritis.
V. (115)...	do.	do.	2	do.	1	1	2	1	0	0	0	0	0	0	Aran-Duchenne type progressive central muscular atrophy.
W. (117)...	do.	do.	0	do.	0	0	0	0	0	0	0	0	0	0	Pernicious anaemia.
W. (118)...	do.	C. Positive.	15	do.	1	1	2	2	1	0	0	0	0	0	Diabetes insipidus; chancre 1 yr. ago.
W. (123)...	do.	Negative.	4	do.	0	0	0	0	0	0	0	0	0	0	Hysteria.
W. (126)...	Not done.	do.	470	do.	0	0	0	0	0	0	0	0	0	0	Mumps, complicating meningitis.
L. (161)...	Negative.	do.	3	do.	0	0	0	0	0	0	0	0	0	0	Post typhoid psychosis.

TABLE II. PURULENT MENINGITIS.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
C. (12)...	Not done.	Negative.	†	Positive.	4	4	4	4	1	2	3	3	3	2	Pink tinge in first 5 tubes.
E. (29)...	do.	do.	†	do.	1	1	1	2	2	3	2	1	1	1	
					1	1	1	1	2	3	3	2	1		
F. (30)...	do.	do.	†	do.	1	1	2	2	3	3	3	2	1	0	Daily administration of meningococcus serum.
					0	0	0	0	2	3	3	3	1	0	Diplococci present at last examination.
					0	0	0	1	2	3	2	1	0	0	Epidemic meningitis.
T. (114)...	do.	do.	†	do.	5	5	5	4	3	2	0	0	0	0	Aortic aneurysm. Autopsy.
					2	2	3	3	3	4	4	4	3	1	

† Countless pus cells.

TABLE III. TUBERCULOUS MENINGITIS.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
C. (15)...	Negative.	Negative.	180	Positive.	2	2	2	3	4	4	2	1	0	0	Tubercle bacilli found in C.S.F.
C. (17)...	Not done.	do.	142	do.	1	1	1	2	3	3	0	0	0	0	Autopsy.
F. (31)...	do.	do.	3000	do.	0	0	0	1	3	4	4	2	1	0	Autopsy. Fluid removed post mortem.
H. (41)...	Negative.	do.	135	do.	2	3	3	1	1	0	0	0	0	0	Bacilli demonstrated.
H. (48)...	Not done.	do.	234	do.	0	0	0	0	1	3	2	1	0	0	Do.
			157	do.	0	0	0	0	1	2	1	0	0	0	
P. (86)...	Positive.	Positive.	86	do.	0	0	0	2	3	3	2	1	0	0	Bacilli demonstrated. Congenital lues & symptoms.
T. (109)...	Negative.	Negative.	126	do.	0	1	1	2	2	2	1	0	0	0	Bacilli demonstrated. Autopsy.
			88	do.	0	1	1	2	2	1	0	0	0	0	
			112	do.	1	1	2	1	1	0	0	0	0	0	
			122	do.	1	1	2	3	3	2	1	0	0	0	

TABLE IV. CONGENITAL LUES.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
B. (7)....	Positive..	Negative.	4	Positive..	1	2	3	3	2	1	0	0	0	0	5 injections Neosalvarsan.
C. (14)...do.....do.....	14do.....	1	1	2	3	3	1	1	0	0	0	2 injections Neosalvarsan.
C. (20)...do.....	Positive..	†do.....	2	3	3	2	1	0	0	0	0	0	Spastic paraplegia.
C. (23)...do.....	Negative.	23do.....	1	2	2	2	2	0	0	0	0	0	
H. (140)...do.....do.....	1	Negative.	0	0	0	0	0	0	0	0	0	0	
M. (70)...do.....do.....	1	Positive..	2	3	3	2	1	1	0	0	0	0	Mongoloid idiot.
S. (101)...do.....do.....	2	Negative.	1	2	3	3	1	0	0	0	0	0	
S. (103)...do.....do.....	1do.....	0	1	2	2	1	0	0	0	0	0	
S. (104)...do.....do.....	21do.....	0	0	0	0	0	0	0	0	0	0	
Y. (127)...do.....do.....	3do.....	1	2	2	1	0	0	0	0	0	0	

† Not done.

TABLE V. SECONDARY LUES.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
Pr. (151)...	Positive..	Negative.	11	Faintly +	0	0	0	0	0	0	0	0	0	0	Condylomata.
F. (32)...do.....do.....	3	Negative.	0	0	1	2	1	0	0	0	0	0	Mucous patches; bone pains.
J. (56)...do.....do.....	13	Positive.	2	3	3	2	1	0	0	0	0	0	Mucous patches; alopecia; papular eruption.
P. (85)...do.....do.....	2	Negative.	1	1	2	1	1	0	0	0	0	0	Papular eruption.
W. (125)...do.....do.....	32do.....	0	1	2	2	1	0	0	0	0	0	Mucous patches.

TABLE VI. TERTIARY LUES.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
J. A. (153)...	Positive..	Negative.	2	Negative.	0	0	0	0	0	0	0	0	0	0	Syphilitic mesaortitis.
C. (16)...do.....do.....	0do.....	2	3	3	3	2	1	0	0	0	0	Lues not suspected.
F. (33)...do.....do.....	2do.....	0	0	0	0	0	0	0	0	0	0	Aortic aneurysm.
G. (37)...do.....do.....	1do.....	2	3	3	2	1	0	0	0	0	0	Gumma of palate.
H. (42)...	Negative.do.....	3do.....	0	0	0	0	0	0	0	0	0	0	Treated several years.
H. (44)...	Positive..do.....	5do.....	0	0	0	0	0	0	0	0	0	0	Latent case.
H. (49)...	Negative.do.....	5do.....	1	2	2	1	0	0	0	0	0	0	Thorough treatment.
J. (155)...	Positive..	Positive..	5do.....	0	0	0	0	0	0	0	0	0	0	Aortic aneurysm.
K. (60)...do.....	Negative.	2do.....	0	0	0	0	0	0	0	0	0	0	
M. (83)...do.....do.....	1do.....	0	1	3	2	1	0	0	0	0	0	Aortic aneurysm.
W. (120)...do.....do.....	3do.....	0	0	0	0	0	0	0	0	0	0	Autopsy; mesaortitis.

TABLE VII. TABES DORSALIS.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
H. (40)...	Positive..	Positive..	135	Positive..	1	1	2	3	3	1	0	0	0	0	
II. (50)...	Negative.	Positive..	94do.....	5	5	5	5	4	1	0	0	0	0	1 intravenous dose of "606" between examinations.
J. (55)...	Positive..	Positive..	38do.....	1	1	2	3	3	1	1	0	0	0	Intra-spinal treatment.
K. (61)...do.....	Negative.	3do.....	1	1	2	2	2	0	0	0	0	0	
L. (65)...do.....	Positive..	35do.....	1	4	2	3	2	1	0	0	0	0	
M. (82)...	Negative.do.....	1	Negative.	3	3	3	2	1	0	0	0	0	0	Treated case.
P. (88)...do.....	Negative.	4do.....	1	1	2	2	1	0	0	0	0	0	Extensive treatment.
P. (90)...	Positive..	Positive..	9	Positive..	1	1	3	3	2	1	0	0	0	0	
R. (94)...	Negative.	Negative.	5	Negative.	1	1	2	3	3	1	0	0	0	0	Treated since 1899.
W. (124)...	Positive..	Positive..	11	Positive..	3	3	4	4	3	2	0	0	0	0	1 intravenous injection of "606" between examinations
			7do.....	0	0	1	1	0	0	0	0	0	0	

TABLE VIII. CEREBRO-SPINAL LUES.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
D. (6)....	Positive..	Negative.	6	Faintly positive.	0	1	3	2	1	0	0	0	0	0	
C. (21)...	Weak positive.do.....	2	Positive..	2	2	3	3	3	3	2	1	0	0	Vigorous specific therapy.
D. (26)...	Positive..do.....	5	Negative.	0	0	0	0	0	0	0	0	0	0	.6 salvarsan previously.
F. (152)...do.....	Positive..	48	Positive..	3	3	4	3	1	0	0	0	0	0	Congenital syphilis.
*F. (34)...	Not done.do.....	†do.....	0	1	3	4	4	3	1	0	0	0	
H. (47)...	Positive..do.....	50do.....	3	4	4	4	3	1	0	0	0	0	Congenital case.
L. (67)...	Negative.	Negative.	3	Faintly positive.	1	1	2	1	0	0	0	0	0	0	Optic atrophy; luetic history.
M. (75)...	Positive..	Positive..	35	Positive..	1	2	2	1	0	0	0	0	0	0	Bilateral abducens palsy.
Q. (91)...do.....	Negative.	7	Negative.	0	0	1	2	1	0	0	0	0	0	Hemiplegia; treated case.
R. (96)...do.....	Positive..	13	Positive..	4	4	4	0	0	0	0	0	0	0	Intra-spinal treatment.
			8do.....	5	4	4	4	3	2	1	0	0	0	
R. (98)...do.....	Negative.	2	Negative.	0	0	0	0	0	0	0	0	0	0	Epileptiform attacks.
R. (99)...	Negative.do.....	27	Positive..	0	0	1	2	1	0	0	0	0	0	Intensive "606" therapy; spastic paraplegia.
T. (113)...	Positive..	Positive..	167do.....	1	2	4	3	2	0	0	0	0	0	Luetic aortitis. No nervous system symptoms.
V. (137)...do.....do.....	9do.....	4	4	3	3	1	0	0	0	0	0	Advanced case.
*W. (144)...do.....do.....	15do.....	1	2	3	1	0	0	0	0	0	0	

† Increased.

TABLE IX. GENERAL PARESIS.

Case No.	W. R. Blood.	Cerebro-spinal fluid.			Gold reaction.										Remarks.
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9	10	
T. (5)....	Positive..	Positive..	57	Positive..	5	5	5	5	5	5	4	2	1	0	
F. (5)....do.....do.....	27do.....	5	5	5	5	4	3	1	0	0	0	
M. (5)....do.....do.....	39do.....	5	5	5	5	4	3	1	0	0	0	
Ba. (5)...do.....do.....	12do.....	5	5	5	5	3	2	1	0	0	0	
Be. (5)...do.....do.....	13do.....	5	5	5	5	5	4	3	2	0	0	
Tr. (5)...do.....do.....	178do.....	5	5	5	5	5	4	2	1	0	0	
P. (5)....do.....do.....	26do.....	5	5	5	5	5	5	4	2	1	0	
II. (5)....do.....do.....	118do.....	5	5	5	5	5	5	4	2	0	0	
G. (6)....do.....do.....	2	Weakly positive.	5	5	5	4	3	1	0	0	0	0	
B. (6)....do.....do.....	6	Positive..	5	5	5	5	5	4	1	0	0	0	
O. (6)....do.....do.....	3do.....	5	5	5	4	3	1	0	0	0	0	
W. (151)...do.....do.....	16do.....	5	5	5	4	3	1	0	0	0	0	

TABLE IX. GENERAL PARESIS.—Continued.

Case No.	W. R. Blood.	Cerebro-spinal fluid.		Gold reaction.										Remarks.	
		W. R.	Cells.	Globulin.	1	2	3	4	5	6	7	8	9		10
S. (151) ..	Positive ..	Positive ..	34	Positive ..	5	5	5	5	4	3	1	0	0	0	
T. (151)do....do....	53do....	5	5	5	4	3	1	0	0	0	0	
*B. (132)do....do....	+do....	5	5	5	5	5	4	2	1	0	0	
*C. (18)do....do....	+do....	5	5	5	5	5	5	4	1	0	0	
*D. (141) ..	Not done.do....	23do....	5	5	5	4	1	0	0	0	0	0	
D. (27) ..	Negative.do....	26do....	5	5	4	3	2	1	0	0	0	0	4 intravenous an intra-spinous treat- ments. Tabo-parc- sis.
			24do....	5	5	5	5	4	3	1	0	0	0	
			7do....	5	5	5	4	3	1	0	0	0	0	
*F (145) ..	Not done.do....	53do....	5	5	5	5	4	2	1	0	0	0	
G. (148)do....do....	138do....	5	5	5	5	5	4	1	0	0	0	Tabo-paresis.
G. (154) ..	Positivedo....	37do....	5	5	5	5	5	4	1	0	0	0	
G. (36)do....do....	40do....	5	5	5	5	5	5	4	3	2	2	Advanced case.
*G. (143)do....do....	42do....	5	5	5	5	4	2	1	0	0	0	
G. (38)do....do....	+do....	5	5	5	5	5	5	5	4	3	1	Advanced case.
H. (139)do....do....	108do....	5	5	5	5	3	2	1	0	0	0	
II. (45)do....do....	7do....	5	5	5	5	2	2	1	1	0	0	Intra-spinous treat- ment. No clinical improvement
			12do....	5	5	5	5	4	3	2	0	0	0	
			10do....	3	3	3	3	2	1	0	0	0	0	
			13do....	2	2	3	3	2	1	0	0	0	0	
J. (54) ..	Positivedo....	28do....	5	5	5	5	5	4	2	1	0	0	
J. (57) ..	Negative.	Negative.	121do....	5	5	5	4	3	2	1	0	0	0	W. R. negative re- peatedly.
K. (58)do....	Positive ..	3do....	5	5	5	5	5	4	3	2	0	0	Blood W. R. positive 5 months previous- ly. Treated case.
L. (147) ..	Positivedo....	24do....	5	5	5	5	3	1	0	0	0	0	
*L. (138) ..	Not done.do....	+do....	5	5	5	4	3	1	0	0	0	0	
*L. (100)do....do....	+do....	5	5	5	5	5	4	2	1	0	0	
*L. (158) ..	Positivedo....	+do....	5	5	5	5	4	2	1	0	0	0	
M. (69)do....do....	43do....	5	5	5	4	3	2	1	0	0	0	Juvenile paresis ; age 5 yrs.
M. (146)do....do....	72do....	5	5	5	5	5	5	4	1	0	0	
P. (87)do....do....	3do....	5	4	4	4	2	1	0	0	0	0	Intra-spinous thera- py.
			9do....	2	2	3	4	3	2	0	0	0	0	
S. (102)do....do....	8do....	5	5	5	5	4	4	3	1	0	0	Intra-spinous thera- py. No clinical im- provement. An ad- vanced case.
			12do....	5	5	5	5	5	4	3	1	0	0	
			7do....	5	5	5	5	4	3	2	1	0	0	
			14do....	5	5	5	4	3	1	0	0	0	0	
*S. (142) ..	Not done.do....	11do....	5	5	5	4	2	1	0	0	0	0	Intra-spinous thera- py.
S. (107) ..	Positivedo....	22do....	5	5	5	5	5	5	4	2	0	0	Intra-spinous thera- py.
			27do....	5	5	5	4	3	2	1	0	0	0	
			4do....	5	5	5	5	4	2	0	0	0	0	
T. (111)do....do....	23do....	5	5	5	5	4	2	1	0	0	0	Intra-spinous treat- ment.
			5do....	5	5	5	5	5	2	1	0	0	0	
			4do....	5	5	5	5	4	2	1	0	0	0	0
T. (112)do....do....	+do....	5	5	5	5	5	4	4	1	0	0	
V. (116)do....do....	30do....	5	5	5	5	5	5	4	3	2	1	Much intra-spinous therapy. No clinic- al improvement.
			25do....	5	5	5	5	5	5	4	2	0	0	
			14do....	5	5	5	5	4	2	1	0	0	0	
			11bo....	5	5	5	4	3	1	0	0	0	0	
W. (119) ..	Weakly positive.do....	17do....	5	5	5	5	4	1	0	0	0	0	Much treatment, with clinical improve- ment.
			20do....	5	5	5	4	3	1	0	0	0	0	
			8do....	5	5	5	3	1	0	0	0	0	0	
W. (139) ..	Positivedo....	62do....	5	5	5	5	4	2	1	0	0	0	
*W. (121)do....do....	+do....	5	5	5	5	5	5	4	1	0	0	
W. (122) ..	Negative.do....	8do....	5	5	5	5	4	4	3	1	0	0	Extensive treatment ; marked clinical im- provement.
			5do....	5	5	5	4	3	1	1	0	0	0	
			6do....	3	4	4	3	1	0	0	0	0	0	
			5do....	1	1	2	1	0	0	0	0	0	0	
W. (136) ..	Positive.do....	22do....	5	5	5	5	5	4	3	1	0	0	
Z. (128)do....do....	44do....	5	5	5	5	4	4	2	0	0	0	Tabo-paresis ; intra- spinous treatment.
			10do....	5	5	5	4	3	2	1	0	0	0	
			9do....	5	5	5	5	3	1	0	0	0	0	
			9do....	5	5	5	4	2	1	0	0	0	0	
A. (1)do....	Negative.	4do....	5	5	5	5	4	3	2	2	1	0	Intra-spinous treat- ment.

*+ Increased.

TABLE X. COMPOSITE TABLE OF RESULTS.

Condition.	Number of cases.	Blood, Wassermann.		Cerebro-spinal fluid, Wassermann.		Phase I.		Gold reaction.	
		Positive.	Negative.	Positive.	Negative.	Positive.	Pleocytosis.	Positive.	Negative.
Miscellaneous group.	60	0	60	C. 4	56	6	8	16	44
Purulent meningitis.	4	Not done	4	4	4	4	0
Tuberculous meningitis.	7	1	6	1	6	7	7	7	0
Congenital lues....	10	10	0	1	9	5	3	8	2
Secondary lues.....	5	5	0	0	5	1	3	4	1
Tertiary lues.....	11	9	2	C. 1	10	0	0	4	7
Tabes.....	10	6	4	7	3	7	5	10	0
Cerebro-spinal lues	15	12	3	8	7	12	8	13	2
General paresis....	49	39	4	47	2	49	43	49	0
		6 not done							

Reaction zone.

Variable, most in lower dilutions. *Verschiebung nach oben*. Upper dilutions; inconstant. Luetic zone.

Do.

Do.

Do.

Do.

Paretic zone.

S. ANALYSIS OF RESULTS.

A. MISCELLANEOUS GROUP.

Most of these cases were punctured with the expectation of finding normal spinal fluid. Seventy-five per cent of them caused no gold precipitation. Where reactions occurred, pathological conditions, presumably sufficient to account for them, were present in a large majority, as may be seen by reference to the detailed reports.

B. PURULENT MENINGITIS.

In two of eight examinations made upon four cases, typical *Verschiebung nach oben* was observed. Two gave reactions analogous to the paretic type, with the noteworthy differences that the supernatant fluid in the low dilutions showed a pink turbidity and the precipitation continued throughout the remaining tubes.

The anomalous result observed in Case F 30 followed repeated injections of antimeningococcus serum.

C. TUBERCULOUS MENINGITIS.

Eleven cases, confirmed either by the finding of tubercle bacilli or by autopsy, gave, with one exception, maximum color changes in the higher dilutions. One observation confirms Eicke's¹⁷ statement that in the early stages the reaction may simulate that of syphilis. As the disease advances there is *Verschiebung nach oben*.

D. CONGENITAL SYPHILIS.

Of ten cases, three showed moderate pleocytosis, five a positive Phase I. Reactions of the luetic type were obtained in eighty per cent.

It is stated by Grulce and Moody¹⁸ that "the Wassermann reaction and other laboratory tests as applied to the diagnosis of congenital syphilis are entirely inadequate, especially in very young infants." In the children's clinic of this hospital, experience has not borne out this statement. Except in the first few days of life, a positive Wassermann reaction can be

demonstrated in the blood in practically every instance, and was present in one hundred per cent of the cases constituting the present series.

E. SECONDARY SYPHILIS.

Reactions in the "luetie zone" occurred in four out of five cases. Eicke reports positive results in 60 of 136 examinations, at times even in the absence of pleocytosis and Phase I. This tends to support the view that syphilis, even in its early stages, is an exceedingly diffuse process, and emphasizes the importance of repeated lumbar punctures on all syphilitics, in the hope of detecting the earliest manifestations of meta-luetic disease.

F. TERTIARY SYPHILIS.

In eleven cases, comprising instances of latent syphilis, gummatous lesions and vascular manifestations, a reaction in the luetie zone occurred in four. In none was there any demonstrable clinical evidence of central nervous system involvement. Several of the individuals were elderly men, who had had their primary infection many years before, and who, in all probability, will never develop cerebrospinal syphilis, tabes or paresis.

G. TABES DORSALIS.

All showed luetie curves. With three exceptions, these were of moderate intensity, yet definite. This is contrary to the statement of Kaplan and McClelland,¹⁹ who find in this group either no reaction at all or at most a very weak one in the first three tubes.

Though clinically a tabetic, Case H 50 may well be in an early stage of tabo-paresis, in which cases we have always found a reaction of the paretic type. In two instances, striking changes in the curves followed minimal amounts of therapy.

H. CEREBROSPINAL SYPHILIS.

Thirteen of the fifteen fluids examined reacted in the luetie zone, six with fairly marked intensity.

Eicke, and Jaeger and Goldstein²⁰ state that the reaction in cerebrospinal lues may simulate that of paresis, differing from the latter in that it appears only after standing for several hours. We have had no difficulty in differentiating the reactions in these two groups of cases.

I. GENERAL PARESIS.

The series exhibits a striking uniformity of results, in that all of the 49 cases gave characteristic paretic curves.

The more advanced cases clinically have shown the most striking tests. M. 69, aged 5, a case of juvenile paresis, gave a typical reaction. That the reaction tends to remain unchanged both during remissions and after intensive intraspinal therapy, is in harmony with the "Wassermann fast" condition of the blood and spinal fluid observed in most instances of this disease. W. 122 alone has shown a marked diminution in the intensity of the gold reaction coincident with outspoken clinical improvement.

9. SUMMARY AND CONCLUSIONS.

1. The colloidal gold test is essentially a laboratory method. It can be performed rapidly and with a minimal amount of spinal fluid.
2. Extreme care in the preparation of reagents and the cleaning of glassware is imperative.
3. Normal fluids give negative reactions.
4. The test is of no aid in the diagnosis of purulent or tuberculous meningitis.
5. It has no advantage over known laboratory procedures in the diagnosis of congenital syphilis.
6. Reactions in secondary and tertiary syphilis are inconstant. Their significance when present is not known. The statement that they indicate the earliest stages of central nervous system involvement lacks proof.
7. The positive reactions observed in the majority of cases of tabes and cerebrospinal syphilis are not characteristic.
8. We feel that the reaction peculiar to paresis is sufficiently constant to warrant its use as an aid in the differentiation of this condition from others with which it might be confused.
9. It is possible that the test may prove to be more sensitive, than are those at present employed, as an indicator of the results of specific therapy in syphilitic diseases of the central nervous system.
10. Much may be expected from the application of colloidal chemistry to the study of biological problems.

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THE ESSENTIAL FEATURES OF ACIDOSIS AND THEIR OCCURRENCE IN CHRONIC RENAL DISEASE.

By ANDREW WATSON SELLARDS,

Assistant Resident Physician, The Johns Hopkins Hospital.

(From the Chemical Division of the Medical Clinic.)

OUTLINE.

- I. General Discussion of Acidosis:
 1. Misuse of the term in the sense of free acid in the blood.
 2. Impoverishment of the body in fixed bases as a basis of the definition of acidosis.
- II. Evidence of Acidosis in Renal Disease:
 1. Clinical picture of air hunger.
 2. Diminution of carbon dioxide in the alveolar air.
 3. Changes in the body fluids:
 - a. Increase in the acidity of the urine.
 - b. Decrease in the titratable alkalinity of the blood.
 4. Increase in the tolerance to bicarbonate.
- III. Evidence that the Increase in Tolerance to Fixed Bases is due to Acidosis:
 1. Determination of carbon dioxide content of the blood.
 2. Titratable alkalinity and rest nitrogen of blood serum.
 3. Comparison of the excretion by the kidney of bicarbonate and those substances whose excretion is suppressed by renal lesions.
 4. Examination of intestinal contents for bicarbonate.
- IV. Evidence that the Essential Feature of Acidosis is an Impoverishment of the Body in Fixed Bases Resulting in:
 1. Decrease in the carbon dioxide of the blood.
 2. Decrease in the titratable alkalinity of the blood serum.
 3. Increase in the tolerance to fixed bases.
 4. Unreliability of the ammonia excretion as a criterion of acidosis.
 5. General methods of detecting acidosis.
- V. Clinical Significance of Acidosis in Renal Disease with Reference to:
 1. Symptoms of uræmia.
 2. Diagnosis of uræmia.
 3. Estimation of degree of acidosis.
 4. Relation to salt action and to therapy.
 5. Considerations of the etiology of the acidosis.

The symptomatology of the commoner types of cardiorenal disease is comparatively well understood as far as the interpretation of the physical signs and symptoms is concerned. In the stage of uræmia, however, a characteristic dyspnœa occurs which has not been fully explained. In a typical case one sees very deep respirations, a tendency to prolonged expiration, and an increase in rate. This is accompanied either by a bright color of the mucous membranes or by a degree of cyanosis so slight that it is wholly out of proportion to the degree of dyspnœa. Similarly, the lungs upon physical examination show nothing to account for the dyspnœa. Such patients soon become drowsy and coma develops eventually. This description represents a classical case in a relatively pure type of renal disease. Such a picture is usually modified more or less extensively by complicating cardiac or pulmonary conditions. This type of dyspnœa is usually described under the term "renal asthma" or "air hunger." The latter term

differentiates it more sharply from "cardiac asthma" and suggests also that the explanation may be the same as in the air hunger of diabetic coma in the sense that it is a dyspnœa due to acidosis. If an acidosis is present during the stage of uræmia, it would explain this dyspnœa very satisfactorily and would also have a fundamental bearing upon the question of therapy in renal disease, especially in regard to the use of neutral salts and alkalies. This paper will consider the explanation of the air hunger occurring in uræmia and the events leading up to the development of this symptom.

GENERAL CONSIDERATIONS IN REGARD TO ACIDOSIS.

The question of acidosis is one of the obscure factors in the chemical pathology of renal diseases. Inasmuch as the theory of acidosis is only in its developmental stage, there are naturally many obstacles in determining whether acidosis develops in the course of nephritis. Consequently, before taking up the discussion of the nephropathies, it is necessary, to analyze and define the fundamental characteristics of acidosis.

Perhaps the one greatest obstacle to the general acceptance of the theory of acidosis consists in a tendency to misinterpret the action of acids in the body. Both in American and in European literature one frequently sees the expression "free acids in the blood" and carbonates administered for the relief of acidosis have been spoken of as neutralizing "acids in the blood," the *freie Säure in dem Blut* of the German literature. In recent years the term "acidæmia" even has been introduced into the literature.

However, it is clearly established that death from acidosis is due to a deprivation of fixed bases. Walter¹ in 1877 showed that the blood in fatal experimental acidosis retained its alkaline reaction toward indicators such as litmus. Benedict² found that the concentration of hydrogen ions in the blood in advanced diabetic acidosis was not materially altered. The therapeutic benefit of the administration of bicarbonate is due to the replacement of carbonates which have been lost and not to the neutralization of any acids circulating in the body. The symptoms accompanying an acidosis are due, not to the presence of free acid in the blood, but to the lack of carbonates and the relief of these symptoms is due to the injected carbonates functioning as such in the blood. Subsequently, they may be neutralized by acid. Furthermore, it is evident that acid may become available more or less rapidly, even within a few hours according to the etiology of the acidosis, for the neutralization of large amounts of alkali. It is clear, however, that the carbonates, upon introduction into the body, do not meet with preformed acid in the circulating blood, for death takes place while the blood still contains alkalies or

alkali-yielding substances. The essential feature of the definition of acidosis has been stated clearly by Naunyn³ under the term *hyppalkalität*, by Emerson,⁴ who uses the term "alkali starvation," and Palmer and Henderson,⁵ who use the term "depletion of bicarbonate from the blood." It would seem necessary, however, to include other tissues, as well as the blood, since, in the absence of evidence to the contrary, it must be considered that there is a general deprivation of the body in bases. It is, of course, possible that there may be a localized increase of hydrogen ions in certain tissues of the body, but in the circulating blood these would always meet with hydroxyl ions for their neutralization. Magnus-Levy⁶ has emphasized especially that in diabetic acidosis there is an increased accumulation rather than an increased formation of acids. A clearer statement of this position would be that there is not even any increased accumulation of acids, but that in acidosis the acids are destroyed largely by neutralization, whereas in health they are destroyed largely by oxidation.

From these considerations it is seen that the underlying principle of acidosis is a general impoverishment of the body in bases. This may be brought about by a variety of methods, such as:

1. Simple starvation; *i. e.*, the withholding of bases from the food.
2. Disturbances of acid formation and elimination.
3. Loss of alkali as such during excessive purgation.

The acidoses have been classified into two groups; namely, the absolute acidoses in which there is an increase in acid, and the relative types in which there is a loss of alkali as such from the body. However, in both cases the end result is the same; that is, there is an impoverishment in bases and not an increase in acid in either case. Consequently, it would seem that there is no real distinction between the so-called relative and absolute acidoses, and that the two conditions are essentially the same. If it is necessary to subdivide the acidoses, they could be classified according to their etiology, or the effects which they produce, but it is not desirable to subdivide the principles upon which the theory of acidosis rests.

EVIDENCE OF ACIDOSIS IN NEPHROPATHIES.

The study of acidosis and the evidence for its occurrence in the nephropathies, will be considered upon the basis which has just been outlined. Among the newer arguments which have been brought forward the most important is the analysis of the alveolar air. Straub and Schlayer⁷ found a definite lowering of the carbon dioxide content of the alveolar air in advanced stages of nephritis. This factor is, of course, dependent upon the carbon dioxide of the blood. It has been studied rather less than the other signs of acidosis and the authors do not draw any final conclusions from their data. Recently, a publication appeared by Lewis, Ryffel, Wolf, Cotton and Barcroft⁸ upon the relation of the carbon dioxide content of the alveolar air to acidosis in cases of cardiac and renal dyspnea. Their data upon this point are much less convincing than those of Straub and Schlayer. Lewis and his associates describe a test based upon the principle that the

percentage of oxygen taken up by the blood under certain standard conditions is controlled in part by the non-volatile acids in the blood. Suggestive results were obtained in certain special cases of dyspnea. In the data, which they report, upon lactic acid in the blood no distinction is made between lactic acid and the lactates.

Porges and Leimdörfer⁹ have also found that the tension of carbon dioxide in the alveolar air is in general parallel to the symptoms of uræmia. However, a lowering of the carbon dioxide tension in the alveolar air cannot be regarded as pathognomonic of acidosis. Porges, Leimdörfer and Markovici¹⁰ report a marked lowering in decompensated cardiac cases.

Henderson and Palmer,¹¹ from a study of the acidity of the urine, came to the conclusion that acidosis is an important symptom in cardiorenal cases. The method used by them consisted in the measurement of the concentration of hydrogen ions in the urine by a series of indicators. The average acidity in a group of cardiorenal cases was higher than the average acidity in a group of normals. The average of a group of nephritic cases was intermediate between the cardiorenal cases and the normal individuals. It is important to note, however, that the extreme values found in cardiorenal cases practically coincided with the extremes found in normal individuals. Expressed as negative logarithms, the extreme normal values vary from 4.82 to 7.45, with an average of 6, whereas the cardiorenal cases range from 4.52 to 7.48, with an average of 5.33.

In considering the signs by which one ordinarily recognizes acidosis in diabetes, it is evident that a true acidosis may exist in nephropathies without conforming to all of the details which are seen in diabetes. With the study of acidosis in various conditions it might be possible to determine the characteristics which are essential in any acidosis and those which are found only under special conditions. In any advanced acidosis one would expect, *a priori*, to find the following features:

I. Examination of Clinical Symptoms:

1. Partial or complete coma.
2. Air hunger.
3. Bright color of the mucous membranes and the venous blood.

II. Diminution of the Carbon Dioxide of the Alveolar Air.

III. Examination of the Blood:

1. Diminution of the carbon dioxide.
2. Diminution of the titratable alkalinity.
3. Relatively constant behavior of the physico-chemical reaction.

IV. Examination of the Urine:

1. Increase in excretion of ammonium salts.*
2. Increase in acidity.

V. Deficit of the Body in Bases (conveniently determined by the increase in tolerance to bicarbonate).

Of this list many features might be absent in mild, or even moderately severe acidoses, and would appear only under extreme conditions. The clinical signs, though very suggestive

* Except in those cases where alkali is lost from the bowel.

are not pathognomonic. The data for the analysis of the alveolar air and the titratable alkalinity of the blood are distinctly suggestive. Almost no data are available upon the carbon dioxide content of the blood. The excretion of ammonia in the urine is normal and there is no striking change in the urinary acidity. In certain types of nephropathy, especially in uræmia, a very striking increase occurs in the tolerance to bases.^{12 13} Two interpretations suggest themselves very readily: namely, (1) an acidosis, and (2) retention of bicarbonate by reason of renal lesions. The explanation of this phenomenon might give conclusive evidence in regard to the presence or absence of acidosis in renal disease. The following points are suggestive of its presence:

1. The clinical signs of acidosis usually develop in typical uræmic stages.
2. Examination of the blood often shows a diminution in titratable alkalinity.
3. The kidney continues to excrete an acid urine even after massive injections of bicarbonate.

The secretion of an acid urine from the neutral or slightly alkaline blood presumably represents a definite functional activity on the part of the kidney, and not a merely passive phenomenon. If one assumes that massive amounts of bicarbonate are accumulating in the blood stream on account of the inability of the diseased kidney to excrete it, then it would be logical to expect that the kidney would cease to excrete acid. Indeed, if an excess of bicarbonate accumulated in the blood stream, then it would be difficult to explain the source from which material could be obtained for the formation of acid. Moreover, in certain cases excretion of bicarbonate may take place readily in the presence of extensive diffuse lesions of the kidney.

On the other hand, there are certain features which are not readily explained on the basis of an acidosis, such as:

1. The normal ammonia content of the urine.
2. The absence of any evidence pointing toward the presence of an excessively abnormal quantity of acids or salts of acids in the urine.

The normal excretion of ammonia points definitely against the existence of an ordinary acidosis. In accordance with this, we find that there is no excretion of any significance of the salts of organic acids, such as would correspond to the excretion of the salts of acetoacetic and β -oxybutyric acid in diabetes. It is questionable, perhaps, whether one is justified in diagnosing an acidosis on the basis of a deficit of the body in available alkalies in the absence of such cardinal signs as an increase in ammonia and in the absence of any disturbance of metabolism with a resulting accumulation of the salts of acids. It seemed desirable to obtain supplementary data in regard to these discrepancies and in regard to the fate of the bicarbonate after injection into the body. The following examinations were carried out:

- I. Examination of urine:
 1. Acidity by Folin's method.
 2. Ammonia coefficient.

II. Comparison of the excretion by the kidney of:

1. Sodium bicarbonate.
2. Lactose.
3. Phenolsulphoneplithalein.

III. Examination of blood:

1. Carbon dioxide content.
2. Rest nitrogen of serum.
3. Titratable alkalinity of serum to Töpfer's reagent and to phenolphthalein.

IV. Examination of the faeces for fixed bases after intravenous injection of bicarbonate.

A partial report of the group of cases upon which these tests were made has already been reported in connection with investigations upon titratable alkalinity. The data for the examination of the urine, the titratable alkalinity of the blood and the tolerance to sodium bicarbonate are taken from Table IV of this former publication.¹⁴ In the present paper the tolerance to sodium bicarbonate is tabulated as deficit in sodium bicarbonate with the understanding that this is the primary factor in the explanation of these cases, though probably it is not the sole factor.

In the determinations of the tolerance to lactose, an initial injection, intravenously, of 2.5 grams was given in cases of ordinary severity. If no excretion took place, this amount was repeated in 6 or 8 hours. In the uræmic and preuræmic cases an initial injection of 5 grams, and occasionally 10 grams, was employed. The lactose was prepared by one heating for 20 minutes at 100° C. in an Arnold steam sterilizer rather than by Pasteurization, as in the routine of Schlayer. Nylander's reagent was used for its detection; the quantity excreted was not determined since it was not used as a functional test, but merely to determine whether its suppression was complete or partial. In the diuresis following the large intravenous injections of bicarbonate, it frequently happened that the urine gave no test for lactose until it had been concentrated to about one-fourth its original volume. When its presence was determined in this way a control was always carried out by concentrating a specimen of urine of the same individual obtained immediately before the injection.

The data for phenolsulphoneplithalein and rest nitrogen were very kindly supplied by Dr. Walter A. Baetjer from his investigations upon nephritis. The rest nitrogen represents the nitrogen measurable by the Kjeldahl process in the alcoholic filtrate from a 1 to 10 mixture of serum in alcohol, the serum being made very faintly acid to litmus. The mixture, after standing for a few minutes, was filtered and the filtrate gave no reaction with the biuret test for proteins.

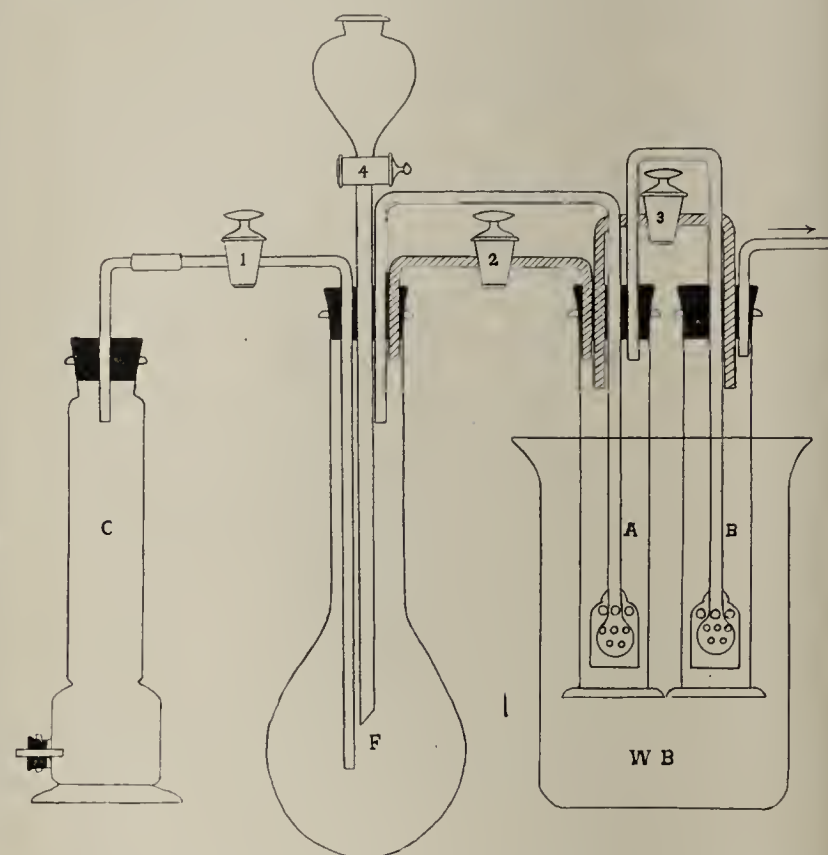
In the uræmic cases which received large intravenous injections, the faeces and, in the cases which came to autopsy, the contents of the intestinal tract, were examined for fixed bases on account of the possibility that with defective kidney function, considerable excretion might be taking place through the intestinal tract. It frequently happened that the specimens were distinctly acid. Some of the specimens contained large quantities of ammonia. These were diluted with water and con-

centrated over the free flame until no more ammonia was given off. The data recorded in the table, therefore, represents the reaction after the removal of ammonia.

The carbon dioxide determinations of the blood are necessary on account of its importance as a sign of acidosis. Inasmuch as an advanced acidosis is required to produce significant changes in the carbon dioxide content, this determination was omitted on many of the less severe cases. Preliminary determinations were made with the Haldane-Barcroft apparatus, designed for the analysis of 1 cc. to 2 cc. quantities of blood. Inasmuch as moderate quantities of blood were available in the ordinary uræmic cases, there was no special advantage in using only minimal amounts. The determinations were carried out by an application of the method of Warburg¹⁵ for minute amounts of carbon dioxide in water. The principle of this method is that carbon dioxide precipitates barium from a solution of barium hydrate as the carbonate. Using a known amount of barium hydrate, the excess may be determined by titration with dilute standard acid in the presence of the precipitated barium carbonate.

Certain modifications of the technique used for water were desirable in working with blood on account of the smaller volumes of material which are available and the higher content of the blood in carbon dioxide. In the first place, certain precautions were necessary for the protection of the blood specimens during their transference from the wards to the laboratory. In order to avoid loss of carbon dioxide, the blood was collected under barium hydrate and the precipitated barium carbonate was subsequently decomposed with acid. Barium hydrate was chosen because of the difficulty of securing carbonate-free specimens of the metals whose hydrates and carbonates are soluble. Throughout the work the standard barium hydrate was protected from the carbon dioxide of the air by a layer of toluene, both in the stock supplies and in the apparatus, during the absorption of carbon dioxide given off from the blood. A layer of toluene (about 1 cm.) was poured into each of the duplicate absorption cylinders. The barium hydroxide was transferred with an ordinary pipette by an open window without any appreciable error from the absorption of atmospheric carbon dioxide during the transference. After the introduction of the barium hydrate under toluene in the absorption cylinders, the entire apparatus was connected up and washed with carbon dioxide free air. For this purpose the apparatus is arranged with a double set of connections, one of which leads through the barium hydrate, the other through the air over it. This makes it possible to wash the apparatus free from carbon dioxide and subsequently, after the evolution of the carbon dioxide from the blood, to wash the gases remaining in the flask into the barium hydrate with carbon dioxide free air. The exact details were as follows: for the collection and measurement of the blood specimens, the neck of a 50 cc. graduated flask was cut off about 2 to 3 cm. above the graduation mark; 30 cc. of 1½% barium hydrate solution was measured into this flask and then tightly stoppered. When the materials are handled rapidly, away from the neighborhood of flames, the error during this pro-

cedure is negligible and it is not necessary to use a protecting layer of toluene. A little more than 20 cc. of blood was taken from a vein in the arm, in the usual way, and discharged into the flask of barium hydrate up to the graduation mark, and with the needle of the syringe dipping under the surface of the barium hydrate. The flask was then stoppered and the mixture thoroughly shaken. The flasks of barium hydrate were kept in the refrigerator before use in order to minimize the error of measuring the blood at a higher temperature than that for which the flask is calibrated. Under these conditions the blood does not clot and, if necessary, the specimen can be kept over long periods before analyzing. It is preferable, however, not to allow it to stand over night, since the precipitated barium carbonate settles out over the bottom of the flask and increases the difficulty of transferring it subsequently.



Twenty cubic centimeters of N/10 barium hydrate were placed in cylinder A and 10 cc. in cylinder B. Each of these was diluted with freshly boiled water to about 75 cc. The water bath was kept at 75° to 80° C. to promote the absorption of carbon dioxide. With the double washing afforded by the Folin absorption tube and with careful heating at the beginning of the evolution of carbon dioxide, complete absorption could be obtained without the use of a third cylinder of barium hydrate. The accompanying diagram illustrates the apparatus at the beginning of the determination. C is a tower, 35 cm. in height, of sodium hydrate sticks; F is an 800 cc. short-necked Kjeldahl flask for the reaction mixture of blood and acid. A and B are the cylinders (22 x 4 cm.) for standard barium hydrate, and WB a hot water bath at 75° to 80° C. With barium hydrate in the cylinders A and B and with the stopcocks in the position shown in the diagram (No 4 closed and 1, 2, and 3 open) suction is applied gently and the apparatus washed for about 30

to 45 minutes to free it from carbon dioxide. Then the suction is stopped and all of the stopcocks are closed. The specimen to be analyzed is washed through the separatory funnel with about 200 cc. of freshly boiled water and followed by about 12 to 15 cc. of 20% orthophosphoric acid. The reaction mixture is then heated for 10 or 15 minutes at the boiling point. This can ordinarily be done without the use of paraffin to prevent foaming. The use of paraffin makes the evolution of steam less regular and increases the tendency of the fluid in the absorption cylinders to suck back. The long absorption tubes projecting above the cylinders were used to lessen the danger from this source. When the heating is finished, the stopcock No. 1 is again opened and a current of air is carried through the apparatus for about 30 minutes. The excess of barium hydrate is then titrated in the absorption cylinders with N/28 hydrochloric acid against phenolphthalein.

The calculation of the results under these conditions is very simple. The burette reading in cubic centimeters subtracted from 84 and multiplied by 2 gives the volumes per cent of carbon dioxide. Eighty-four is the equivalent in N/28 solution of 30 cc. of an N/10 solution. The cubic centimeters of N/28 solution neutralized by the carbon dioxide, when multiplied by 0.4, gives the cubic centimeters of carbon dioxide at 0° C. and 760 mm. in 20 cc. of blood. (One cubic centimeter of an N/28 solution for reaction with barium hydrate is equivalent to 0.4 cc. of carbon dioxide under standard conditions.) This product multiplied by 5 gives the cubic centimeters of carbon dioxide in 100 cc. of blood, or the volumes per cent of carbon dioxide.

The accuracy of this method was tested upon 20 cc. quantities of a solution of sodium carbonate containing 45 volumes per cent of carbon dioxide (N/25), and upon normal human blood. The analyses of the carbonate solutions were accurate in actual practice to within 3 to 5 volumes per cent though test cases could be run a little closer. The relative error is comparatively large though the absolute error is small. The following analysis illustrates this:

	Calculated	Found	Error in volumes %
Grams CO ₂	0.0176	0.0164	
Volumes %	45	42	3

The analysis of six specimens of normal venous blood gave values ranging from 44 to 52 volumes per cent.

A brief synopsis of the clinical data is given in the table in order to provide a general impression of the type of cases on which these tests were made. Of the patients who showed heart lesions, all were tested at a time when the compensation was good. Those who were subject to frequent breaks were tested after an interval of not less than two or three weeks after the last break. All of these cases were given a normal mixed diet at the period when these tests were made with the exception of the uræmic patients. In the stage of uræmia, the intake of carbohydrates was usually limited but it was not reduced sufficiently to give rise to acetonuria in any instance. The tests for acetone with sodium nitroprusside were negative in all of the cases in the table on pages 148 and 149.

ANALYSIS OF TABLE I.

Comparison of the Behavior of Bicarbonate with Substances which are Suppressed by Renal Lesions.—This table illustrates several important features. In the first place, the excretion of bicarbonate is essentially different from those substances which are suppressed during renal insufficiency. In addition to the substances recorded in the table, all of these patients were excreting a certain amount of chlorides even upon a diet in which the chlorides were restricted. However, the chlorides, lactose, phenolsulphonephthalein and the water, were not completely suppressed, even when the intake of these substances was comparatively small in amount. Thus not more than 10 grams of lactose, nor more than 0.0012 gram of phenolsulphonephthalein were required in the most severe cases to produce some excretion in the urine. On the other hand, the bicarbonates were often completely suppressed even in quantities as high as 160 grams. This establishes a rather sharp difference between the bicarbonate and a fairly representative group of substances which are known to be suppressed by renal lesions; namely fluids, salts, sugars and dyes.

Carbon Dioxide Content of the Blood.—The content of the venous blood in carbon dioxide is sufficiently low to be practically pathognomonic of acidosis. In four typical cases the values varied from 10 to 24 volumes per cent as compared with a normal of 44 to 52 volumes per cent. Under the conditions which occur in uræmia it is difficult to explain this reduction by other factors.

Ammonia Excretion.—The ammonia excretion in the cases uncomplicated by hepatic lesions is distinctly normal. This at once raises the question as to whether there is no increase in the accumulation of ammonia, or whether it accumulates in the blood by reason of renal insufficiency. Comparatively large amounts of ammonia were found in the intestinal tract in the examination of the feces for fixed bases. This might appear to lend superficial support to the view that this ammonia is excreted by way of the intestinal tract by reason of renal insufficiency. On account of the accumulation of urea in the body and its excretion into the intestine, this ammonia can be accounted for much more logically by the fermentation of urea. Furthermore, the values for the rest nitrogen of the blood practically excluded the accumulation of any significant quantity of ammonia in the blood, which would in any way be comparable to the excretion of ammonia in even moderate grades of diabetic acidosis. Thus, in three cases (H, K, and M) the values for rest nitrogen fall within normal limits although the tolerance to bicarbonate is definitely increased. Moreover, in those cases where the rest nitrogen is high this increase can be accounted for largely by the increase in the urea fraction. The investigations of the French school have shown that urea is quantitatively the most important constituent of the rest nitrogen, both in the normal and in nephritic individuals. Weill has recently reviewed this subject.¹⁰

Reaction of Feces.—The reaction of the feces is important. It demonstrates that the injections of bicarbonate were retained within the body. In some cases the intestinal contents were

acid. In Case A, who received in all 160 grams of bicarbonate, an alkaline reaction of the feces was not obtained after any of the injections or at section. In another patient, D, in whom 70 grams of bicarbonate were injected, the intestinal contents at section were found to be slightly acid to litmus. No free ammonia was present in these specimens.

Effect on Clinical Symptoms.—Observations on the effect of the administration of bicarbonate were made with especial reference to three features, namely: coma, dyspnoea, and the total output of urine. Of the seven cases in uræmia, five were sufficiently comatose to be either practically or wholly unable to respond to simple questions. In one of these, B, there was no change in his mental condition. Of the other four, one came out completely from the uræmia, though this result was probably not to be attributed to the bicarbonate. In the other three there was distinct improvement in the mental condition, which could be directly attributed to the injections, though none of these recovered completely from their stupor. The improvement was shown by a diminution in their restlessness and by their ability to answer questions, and even to carry on a limited conversation. In one patient, C, the improvement appeared within a few hours after the administration of 30 grams of bicarbonate, whereas in another, A, no change was noted till 100 grams had been injected. The air hunger which existed in three cases (A, C and D) was definitely relieved by the injections. The respiratory changes in two patients (H and J) were especially interesting. These men had continual dyspnoea which did not disappear even upon rest in bed. However, after the administration of bicarbonate, this dyspnoea disappeared completely and did not return during the several weeks that they remained in the hospital. In a third case (L) the dyspnoea was not affected by an amount of bicarbonate sufficient to render the urine alkaline.

The effect upon the excretion of urine was not especially noticeable in the cases with a normal output. In the cases with oliguria the output improved as a rule, though exact measurements were often very difficult on account of the incontinence of many of these patients. In two instances (A and D) a definite polyuria followed the injections, and in a third case, with anuria of 15 hours duration, a polyuria developed within 8 hours after the injection.

SUMMARY OF THE DATA IN TABLE I.

In summarizing this evidence, then, we have a striking increase in the tolerance to fixed bases in many nephritics. The parallelism between this increase in tolerance and the impoverishment of the blood in titratable alkali is crucial evidence of a marked deficit of the body in bases or in substances which readily give rise to bases. This deficit is often sufficient to give rise to definite clinical symptoms. In four cases of uræmia, the carbon dioxide content of the blood was markedly lowered. These features justify the diagnosis of an acidosis of high grade on the basis that the essential feature of acidosis is an impoverishment of the body in bases or in substances which readily give rise to bases. Such an acidosis is characterized by:

1. An increase in the tolerance to bases.
2. Decrease in the titratable alkalinity.
3. Decrease in the carbon dioxide content of the blood.
4. Normal excretion of ammonia.
5. Absence of any disturbance of carbohydrate or fat metabolism.

The question was raised as to whether the bicarbonate injected in the uræmic cases is retained as such, or whether it is retained on account of an acidosis. It is seen that this question requires a little modification. In any case, even in an acidosis the bicarbonate which is injected is retained as such, that is for use as an alkali. The point at issue, is whether the bicarbonate is retained in considerable excess over the normal content of the blood on account of the failure of the kidney to excrete it, or whether it is retained to replace a deficit of carbonates in the blood and other tissues. The latter explanation is clearly the correct one. It seems probable that after the urine has been rendered alkaline by bicarbonate, an insignificant amount might be retained on account of renal suppression; but practically all of the bicarbonate is retained to restore the content of the tissues to normal.

DEFINITION OF ACIDOSIS.

A priori, it is to be considered that an increase in the excretion of ammonia is an essential feature of acidosis. However, there are cases of nephritis and uncomplicated diabetes which show a definite change in the titratable alkalinity and a significant increase in their tolerance to bicarbonate without an increase in ammonia. Such cases justify the conclusion that an acidosis is not necessarily accompanied by an increase in the excretion of ammonia. The changes from the normal metabolism to a state of acidosis are purely quantitative. It is evident that there is no natural division, and any such division in the early stages would necessarily be purely artificial. By definition, then, an acidosis is a general impoverishment of the body, from any cause, in fixed bases or in substances which readily give rise to fixed bases. The essential fundamental features that have been established thus far which would be common to all acidoses are:

1. An increase in the tolerance of the body to fixed bases.
2. A diminution of the titratable alkalinity of the blood serum.
3. A diminution of the carbon dioxide of the blood.

These are the features which are well understood and are readily susceptible of demonstration. They would, of course, be accompanied by related changes; a low carbon dioxide content of the blood should result in a low tension of carbon dioxide in the alveolar air, an analysis which is not always satisfactory in a comatose patient, or in one who is, for any reason, unable to co-operate. Similarly, the reduction of the titratable alkalinity might be accompanied by a slight increase in the excretion of neutral salts in the urine, but it is evident that it might readily be well-nigh impossible to detect this change in excretion. The ammonia content of the urine is by no means an absolute criterion of the presence or absence of acidosis. It may be normal even in moderate grades of dia-

betic acidosis. On the other hand, the relative and absolute amounts of ammonia may be comparatively high in certain toxæmias in which acidosis is absent; a toxæmia of pregnancy was reported in which the daily output of ammonia was as high as two grams and the coefficient reached 40% under conditions in which acidosis could be excluded.¹² There is one condition which definitely would not come under this definition of acidosis; namely, the localized accumulation of acid in special organs or tissues, such as Fischer¹⁷ has described as occurring in the kidney.

Two methods are available for the detection of these features of acidosis; namely, the reaction of blood serum to phenolphthalein and the effect of the ingestion of sodium bicarbonate upon the reaction of the urine. These methods have given evidence of acidosis of varying grades in diabetes, in nephropathies, in anæmias, and in rheumatic fever. Either of them would presumably be applicable in the detection of acidosis from any cause whatever. The details of these tests are very simple. For the first, 1 cc. of serum is added to 25 cc. absolute alcohol and the mixture shaken thoroughly. The precipitated proteins are filtered off and the alcoholic filtrate, without washing the precipitate, is evaporated to dryness with a few drops of phenolphthalein solution, taking care to avoid dilution of the alcohol from an excess of steam during evaporation. In the earliest changes from the normal the alcoholic filtrate becomes red, but the residue after evaporation rapidly loses its color at the temperature of the water bath (5 to 15 minutes), whereas the normal specimens retain their color for several hours. Details of the more advanced changes are given in reference No. 14.

The test by means of sodium bicarbonate is equally simple. Five grams of sodium bicarbonate are given by mouth unless gastrointestinal complications that would interfere with absorption are present. In that case intravenous injection may be used. Preferably, the patient should void at the time of administration of the bicarbonate. Practically any normal individual, on an ordinary mixed diet, will react, usually in about 3 hours, by excreting a urine which is neutral or alkaline to litmus. When a specimen does not react sharply to litmus paper, a few cubic centimeters should be thoroughly boiled in a test tube to promote the change of bicarbonate to normal carbonate. Specimens which are faintly acid to litmus before boiling may react slightly alkaline to litmus after boiling. In cases which do not react the bicarbonate may be repeated in increasing quantities such as 20 or 30 grams at intervals of 3 to 6 or 8 hours, the reaction of the urine being tested before each repetition. In some cases massive quantities may be given without affecting the reaction of the urine, *e. g.*, 150 grams in 1 to 2 days.

It is possible in a general way to determine the physiologic effect of various grades of depletion in bicarbonate. A deficit of as much as 20 grams can be detected by the examination of the blood, but certainly does not give rise to any symptoms. A deficit of approximately 40 grams causes a sharper change in the behavior of the blood, but still does not give rise to any appreciable dyspnoea even on exertion. With an in-

crease in this deficit to 70 or 80 grams, three patients showed dyspnoea which persisted in two of them, even when at rest in bed. It is difficult to determine even the approximate quantities which would cause the more advanced symptoms of stupor and coma, since other factors often contribute to the production of these symptoms. In two cases which were observed a condition of air hunger and partial coma was relieved temporarily by the injection of 130 and 160 grams respectively. It seemed clear that this deficit would have been the immediate cause of death in these cases and one may assume that such quantities approach the limits which would be fatal in the depletion of the body in fixed bases. These figures are slightly lower than the highest values obtained in diabetic coma in which a deficit of 200 grams has been reported.¹⁸ The interpretation of the figures in diabetes is complicated by the rapid formation of acid and the compensatory neutralization by ammonia. In fatal cases it seems probable that the unexhausted supply of fixed bases is only a minimal quantity; therefore, it would not be surprising to find that the total available supply of substances in the body yielding fixed bases is in the neighborhood of the equivalent of 200 grams of sodium bicarbonate, or at least of that general order of magnitude.

CLINICAL SIGNIFICANCE.

There are several factors bearing upon the significance of the acidosis observed in these cases. In the uræmic cases, the severity of the condition of the individual patients was by no means proportional to the degree of acidosis. In some patients the lack of carbonates was extreme, while in others the deficit was so slight that no symptoms of dyspnoea developed. In one case (L) the dyspnoea was not typically cardiac and was apparently of renal origin yet it was definitely not due to acidosis. From these considerations, it seems evident that acidosis is only a secondary factor and that it is the result, and not the cause, of the renal lesions. However, it does not develop merely as a terminal event, but is present in an appreciable degree in ordinary grades of nephritis. The evidence at hand shows that there may be definite signs of chronic interstitial lesions, accompanied by moderate subjective symptoms without any appreciable grade of acidosis. On the other hand, it is equally definite that an acidosis sufficiently severe to produce symptoms of dyspnoea may develop at least many months before any signs of uræmia appear. Furthermore, this acidosis may be so extensive as to play an important rôle in the symptomatology of uræmia and even to constitute the immediate cause of death. That it is seldom, if ever, the sole cause of death is strongly indicated by the merely transient benefit following the injection of bicarbonate in the uræmia of chronic cases. Some of the symptoms resembling toxæmia in uræmia are due, not altogether to the presence of a foreign toxin, but in part to the depletion of the body in one of its normal constituents. Therefore, the therapeutic bleeding for the removal of any toxins that may be circulating in the blood causes at the same time a still further diminution of a substance which is already seriously depleted. This disadvantage could be

TABLE I. EXAMINATION

CLINICAL RECORD.							Urine.			
Case.	Age.	Respiration with regard to dyspnœa.	Heart.	Sclerosis of arteries.	Average blood pressure (mm. of Hg.).	Edema.	Fluid balance (average daily output).	Acidity in % of N/1 solution.	Ammonia coefficient.	Deficit in sodium bicarbonate (grams).
A.....	48	Air hunger....	Hypertrophied, compensating.	Well marked	190	Polyserositis..	500 cc	3.5%	3.0%	160+
B.....	29	Well-marked dyspnœa.	Normal	Moderate...	140	Well marked..	Normal....	2.3%	3.5%	40+
C.....	60	Air hunger....	Well marked hypertrophy, compensating.	Well marked	180	None	Anuria 15 hrs.	30+
D.....	57	Air hunger....	Hypertrophied, compensating.	Well marked	220	None	Coming oliguria.	1.5%	2.4%	70
E.....	64	No air hunger. Moderate dyspnœa.	Hypertrophy. Frequent breaks	Well marked	240	Well marked..	Normal....	3.8%	5.2%	30
F.....	40	None	Hypertrophied, compensating.	Moderate...	210	None	Polyuria...	2.7%	4.0%	30
G.....	40	No dyspnœa...	Normal	Well marked	180	Slight	Oliguria....	2.5%	3.5%	40

EXTREME CASES WITH

H.....	55	Frequent attacks of dyspnœa.	Hypertrophied, dilated. Frequent breaks.	Moderate...	170	Moderate	Oliguria 500 cc.	3.0%	3.7%	70 ²
I.....	40	Dyspnœa on exertion.	Hypertrophied, compensated.	190	Slight	Normal....	3.1%	4.2%	80 ²
J.....	44	Constant dyspnœa.	Hypertrophied, dilated. Frequent breaks.	Well marked	200	In lower extremities.	Polyuria...	2.5%	2.6%	70 ²
K.....	35	None	Partially compensated on admission.	140	Well marked..	Polyuria...	2.0%	8.7%	80
L.....	52	Constant. Well marked.	Dilated. Partially compensated on admission	Slight.....	160	Moderate	Normal....	2.0%	11.6%	40

OUTSPOKEN CASES WITH MOR

M.....	41	Cheyne-Stokes, with marked dyspnœa.	Frequent breaks.....	Well marked	170	Well marked..	Polyuria...	4.0%	7.1%	30 ²
N.....	49	Slight dyspnœa	Acute mitral endocarditis.	Moderate...	140	Moderate	Normal....	1.5%	11.8%	30 ²
O.....	67	Normal.....	Hypertrophy, compensated.	Slight	160	Puffiness, face.	Normal....	2.7%	3.0%	20 ²
P.....	54	Normal.....	Slight hypertrophy....	Moderate...	190	Puff'n's, eyelids	Normal....	2.4%	2.2%	10 ²
Q.....	39	Normal.....	Slight hypertrophy, compensating.	Moderate...	200	None	Normal....	1.8%	4.0%	10 ²
Normal average.								1% to 3%	2% to 5%	5

¹ No color after 5 minutes.² By inges

EFFUSE NEPHROPATHIES.

RENAL FUNCTION.									
Excretion of phenolphthalein (% in 2 hrs.).	Blood.	Blood serum.						Reaction of feces to litmus after removal of NH ₃ .	Subsequent record (or pathological diagnosis).
	% of CO ₂ .	Rest nitrogen grams per liter.	Alkalinity to Töpfer's in % N/1 solution.	Behavior toward phenolphthalein.			1 to 10 dilution of whole serum in water.		
				After removal of protein.					
				In alcoholic solution.	Residue after evaporation.	In aqueous solution.			
18% ³	20%	2.1	0.6%	No color...	No color...	No color...	No color...	Neutral or acid	Death two days later. Chronic diffuse nephritis.
Trace...	10%	2.0	0.9%	No color...	No color...	Pink.....	Red	Neutral.....	Death one day later. Acute exacerbation of chronic diffuse nephritis.
Trace...	24%	0.6%	No color...	No color...	No color...	Pink.....	Slightly acid...	Slight cardiac hypertrophy. Death one day later. Chronic diffuse nephritis.
Trace ⁴ ..	22%	0.8%	No color...	No color...	No color...	No color...	Slightly acid...	Death three days later. Chronic diffuse nephritis.
35%	0.5	0.8%	Pink.....	(¹)	Red	Red	Neutral.....	Recovery from uræmia. Death six weeks later with broken compensation and early bronchopneumonia. Chronic diffuse nephritis.
Trace...	0.6	0.7%	No color...	No color...	Pink.....	Pink.....	Left hospital in serious condition.
Trace ⁴	0.8%	Pink.....	(¹)	Red	Red	Death three days later.

EFFECTIVE SYMPTOMS.

35%	39%	0.3	0.6%	No color...	No color...	Pink.....	Red.....	Slightly alkaline.	Death eleven months later. No section.
35%	35%	0.7	0.8%	No color...	No color...	No color...	Red.....	Slightly alkaline.	Left hospital after six weeks without subjective symptoms when at rest.
Trace...	35%	1.0	1.0%	No color...	No color...	No color...	Faint pink.	Slightly alkaline.	Death eight months later. No section.
50%	0.2	0.8%	No color...	No color...	Red.....	Red.....	Slightly alkaline.	Death three months later. Early luetic hepatitis. Chronic diffuse nephritis. Positive Wassermann.
.....	0.7%	No color...	No color...	Red.....	Red.....	

THE SUBJECTIVE SYMPTOMS.

25%	42%	0.2	0.9%	Red.....	(¹)	Red.....	Red.....	Diffuse cirrhosis liver.
20%	51%	1.0%	Red.....	(¹)	Red.....	Red.....	
25%	42%	1.0%	Red.....	(¹)	Red.....	Red.....	
35%	0.8%	Red.....	Red.....	Red.....	Red.....	
.....	1.3%	Red.....	Red.....	Red.....	Red.....	
65%	45% to 50%.	0.3	1.0%	Red.....	Red.....	Red.....	Red.....	

fore death. ⁴ After 0.0012 gram.

readily obviated by the injection of bicarbonate though special precautions might be necessary in the many cases where the bleeding is done primarily for the relief of some mechanical embarrassment to the circulation.

Diagnosis of Uremia.—The wide variation in the degree of acidosis in these cases of uræmia raises the question as to whether cases may not occur in which it is absent altogether. No such instances have been encountered; the readiness with which slight grades of acidosis can be detected, and the frequent appearance of the milder grades, even in cases of only ordinary severity, would indicate that chronic uræmias without any acidosis would be at least comparatively rare. In the diagnosis of uræmia there is often an opportunity for considerable variation of opinion. The similarity of the symptoms which may result from cardiac, renal, and cerebral lesions sometimes renders differentiation rather difficult; in complicated cases where changes in all of these organs are present, it may be impossible to determine what features predominate. It seems probable that metabolic changes occur in these cases which can be correlated with the clinical features. The examination of the blood and urine for such factors as the titratable alkalinity, rest nitrogen, and the renal function in conjunction with the clinical picture might enable one to differentiate more sharply certain types of these cases. The cases of uræmia reported in this paper were by no means free from cardiac and cerebral complications, but only those types were selected in which the uræmic symptoms predominated very definitely.

Clinical Estimation of the Degree of Acidosis.—Several methods have been proposed for the rapid clinical estimation of the degree of acidosis in diabetes. A review of this subject by Addis¹⁹ appeared recently. They depend, for the most part, upon the simplified methods for estimating β -oxybutyric and acetoacetic acid or acetone. Obviously, such methods are particularly applicable to diabetes. In renal disease, as a preliminary step, the examination of the titratable alkalinity is desirable, since it gives information at once as to whether the administration of bicarbonate is urgent and also an idea of the amount which will be required. The determination of the tolerance to bicarbonate combines in one step a measure for therapy and a method for comparing the extent of acidosis in different individuals.

Relation of the Acidosis to Salt Action and to Therapy.—In considering the treatment of the acidosis of nephropathies one may ask how much good may be expected and also what dangers there may be from the use of the comparatively large amounts of salt that are often necessary, on the basis that the effect of salt in the production of œdema is due to the general properties of salt action. In regard to this latter point it is important to remember that one is not increasing the carbonates above the normal, but merely replacing a deficit of this salt. It is important to know the effect of bicarbonate upon the excretion of urine, the production of œdema, and the work of the heart. As regards the excretion of urine, there is a definite tendency of the bicarbonate to cause an increase in the total output. It might be expected that in the advanced uræmias the injection of massive doses of bicarbonate during

a period of one to two days would tend to produce an œdema. However, the fluid balance was not disturbed, or else a polyuria resulted. In cases where there was a pre-existing œdema, there was no tendency for it to increase or diminish. When acidosis develops in the uræmia of chronic renal disease its treatment by massive injections of bicarbonate offers not more than relief from air hunger and temporary improvement in the mental condition and general comfort of the patient. The effect on uræmia of the early treatment of acute nephritis can best be studied in Asiatic cholera. In this disease acute nephritis occurs in all severe cases and uræmia develops with surprising regularity. Where treatment was instituted early in the course of the disease it was found that no deaths from uræmia occurred in a series of 76 cases, whereas in a corresponding control series there were 10 deaths from uræmia.²⁰ On the other hand, the chronic nephritides extend over such a long period of years that it would be extremely difficult to determine the effect, in regard to the subsequent development of uræmia, of the early administration of therapy before the signs of an outspoken acidosis had appeared. The treatment of the early grades of acidosis would be a simple and rational procedure and would seem to offer some possibility of exerting a favorable influence upon such a slowly progressive condition as chronic nephritis.

It is obviously necessary to establish the existence of acidosis in each individual patient in preference to the routine treatment of all cases as recommended by v. Hösslin.²¹ This is readily accomplished, either by the examination of the blood serum with phenolphthalein, or by the administration of increasing quantities of bicarbonate until an alkaline reaction of the urine is produced. The choice of carbonates for administration is important, especially for intravenous injection. The normal carbonate destroys red blood corpuscles rapidly in vitro, causing extensive hæmolysis and discoloration of hæmoglobin, even in the presence of serum. While such action probably does not take place in vivo, yet it is conceivable that less evident injury may occur. One argument which has been advanced in favor of the normal carbonate is that it can take up additional carbon dioxide, relieving the internal respiration, whereas the bicarbonate cannot take up any additional carbon dioxide. However, this would not seem to be important, since the bicarbonate, on passage through the lungs, gives off carbon dioxide and can then take up more from the tissues for transportation to the lungs. Weight for weight, sodium bicarbonate neutralizes only about five-eighths as much acid as the carbonate. Concentrations of 4 or 5%, however, cause no hæmolysis of washed red corpuscles in vitro, whereas, fractions of a per cent of the carbonate are very active against red cells producing hæmolysis and discoloration of the hæmoglobin even in the presence of serum. Accordingly, very much stronger solutions of bicarbonate can be used than would be advisable with the normal carbonate. The relatively long duration of the effect of bicarbonate²² is a hopeful feature in therapy of nephritic conditions as contrasted with the short duration in diabetic coma.

Treatment of acute nephritis by the injection of massive

doses of carbonate and neutral salt was carried out by Hogan and others at the suggestion of Fischer.¹⁷ These injections have been performed on the basis that an acidosis occurs in all acute nephritides without determining its existence in the individual patients. Furthermore, the quantity to be administered was determined by the clinical symptoms without reference to the reaction of the urine. More recently Fischer²² has suggested that the reaction of the urine be followed as a guide to the quantity of carbonate to be administered. In this paper I have not considered the relief of nephritis by the employment of salt action *per se*. The conclusions which have been obtained in regard to acidosis differ from those of Fischer in two respects; namely, (1) that a localized accumulation of hydrogen ions in certain organs or tissues of the body is not considered to be an acidosis in the generally accepted sense of the term, and (2) the impoverishment in bases which reaches its maximum in uræmia represents an effect and not the cause of the renal condition.

Etiology.—In considering the etiology of this acidosis of renal disease it is evident that the carbonates are depleted not by their loss as such from the body, but through chemical action. The only logical possibility of their destruction by chemical action is through neutralization by acids. The most obscure factor is the source from which such acids could come. No evidence appears in the literature of the presence of any abnormal acids or salts of acids in the blood or urine of nephritic cases. One of the normal functions of the kidney is the production and excretion of acids from a neutral or slightly alkaline blood. With the impairment of the other functions of the kidney it seems not unlikely that this functional activity is also impaired, with the result that there is a very gradual decrease in the excretion of acid in the urine and a corresponding reduction of carbonates in the blood corresponding to the amount of acid salts which are suppressed. Such an explanation would account for the long duration of the effect of the administration of carbonates in renal disease as contrasted with diabetes. It is noteworthy that the extent of the acidosis is roughly parallel to the signs of renal suppression. In Table I the cases which show a high deficit in bicarbonate also show definite retention of rest nitrogen. In some of the parenchymatous nephritides Baetjer²³ has found evidence of increased permeability of the kidney; the parenchymatous type of case shows no evidence of acidosis. The excretion of ammonia is also interesting. In diabetes the high ammonia values of the urine result, not from an increased formation of ammonia, but from an interception and neutralization of ammonia in the tissues by acid during the process of the formation of urea. In the nephropathies, however, it is quite possible that in the blood stream there would be no ammonia available for the neutralization of the acid salts which the kidney fails to excrete. As these salts tended to accumulate in the blood neutralization by the carbonates would take place. The following is a summary of the points which lend support to the view that this deficit of the body in bicarbonate is due to an impaired activity of the kidney in its function of excreting acids:

1. The signs of acidosis are proportional to the signs of renal suppression.
2. The effect of the administration of carbonates lasts for comparatively long periods.
3. The normal excretion of ammonia could be explained by the lack of any considerable quantity of ammonia in the blood stream which could be intercepted by acids.

On this basis one would expect to find the acidity of the urine decreased rather than increased in chronic renal disease. Henderson and Palmer²⁴ have carried out extensive examinations of the hydrogen ion concentration of the urine and their observations do not support this view very strongly. The average acidity in a group of renal cases without cardiac decompensation was slightly higher than the normal average, but not so high as the average in a group of decompensated cardiorenal cases. Of the individual cases, three were found to be at the lower limits of normal, while the remaining 11 cases were all higher than the normal average, but only one occurred which was higher than the normal maximum.

It is noteworthy that even after very extensive destruction of the renal tissue with a marked impairment of practically all of its functions, the organ still retains its ability to excrete acids in a remarkable degree. Patients in fatal uræmia, developing in the course of a chronic or acute nephropathy, continue to excrete a urine of distinctly acid reaction. Indeed, it seems that fixed bases are excreted only when they are introduced into the body in excess. The ability of the kidney to excrete acid salts is apparently one of the last functions to be lost, persisting as long as fluid is excreted.

CONCLUSIONS.

I. The essential feature in acidosis consists in a general impoverishment of the body in bases or in substances which readily give rise to bases; *e. g.*, sodium carbonate. The impoverishment in bases may be brought about by the loss of bases as such, as in the so-called relative acidosis, or by the neutralization by acids as in the so-called absolute acidosis. In either case the end result is the same and the distinction between relative and absolute acidosis is misleading.

II. The fundamental features of every acidosis which have been established thus far are:

1. An increase in the tolerance of the body to fixed bases.
2. A diminution in the titratable alkalinity of the blood serum.
3. A diminution in the carbon dioxide of the blood.

III. The excretion of ammonia either in its relative or absolute amounts does not afford a definite basis for the detection of acidosis. Thus:

1. The ammonia excretion may be normal in acidosis. This may occur in diabetic cases which are free from any suggestion of renal disease. In the nephritic cases in which the ammonia is low in the urine it is probable that there is no increase in the quantity of ammonia in the blood though some have suggested that it accumulates in the blood and its excretion in the urine is suppressed.

2. The ammonia excretion may be increased even to the extent of 2 grams per day with an ammonia coefficient of 40%, in conditions in which there is no acidosis.

IV. An acidosis of high grade occurs in certain nephropathies. The acidosis reaches its maximum in the uræmia of acute and of chronic diffuse nephropathy. It is not a terminal event, for it is often present in relatively high grade in outspoken cases many months before the development of uræmia. It represents the effect rather than the cause of the renal lesions and thus constitutes a condition of only secondary importance.

V. The characteristics of the chemical pathology of this acidosis are:

1. Increase in tolerance to bases.
2. Decrease in titratable alkalinity of the blood.
3. Decrease in the carbon dioxide content of the blood.
4. Normal excretion of ammonia.
5. Absence of any disturbance of carbohydrate or fat metabolism, and absence of the salts of any abnormal organic acids.

VI. The changes in the titratable alkalinity of the blood which can be detected by the use of phenolphthalein afford a ready means for the prompt diagnosis of acidosis and the method is particularly applicable in renal disease. In this condition it furnishes a definite indication of the amount of bicarbonate that will be required for the relief of the acidosis. The determination of the tolerance of the body to sodium bicarbonate also affords a delicate method of general application for the detection of acidosis.

VII. Examination of the fæces showed that bicarbonate was not excreted into the intestine even in the cases in which massive doses were injected.

VIII. Some of the toxic symptoms of uræmia are due, not to the presence of a toxin, but to the absence of a normal constituent of the blood, namely, the carbonates. Therefore, the therapeutic bleeding for the removal of any toxins that may be circulating causes at the same time a still further diminution in a substance in which the blood is already seriously depleted. This disadvantage could be readily obviated by the injection of bicarbonate at the time of bleeding.

IX. This acidosis is perhaps the result of defective function of the kidney in the normal separation and excretion of acid salts. If this supposition is correct, the acidosis would be an *indirect expression* of renal retention. In support of this it has been found that the acidosis is in general parallel to the ordinary signs of renal retention, such as the suppression of the excretion of dyes and sugars and the accumulation of non-protein nitrogen in the blood.

DISCUSSION.

This evidence of acidosis offers a satisfactory explanation for some of the clinical symptoms which occur in uræmia. The coma in some cases is due to an impoverishment of the

body in bases and can be partially relieved by the injection of bicarbonate. In uncomplicated cases the typical air hunger which sometimes develops and the accompanying bright color of the mucous membranes is another expression of acidosis.

In the acute nephritis of Asiatic cholera, the early administration of massive injections of sodium bicarbonate results in permanent benefit. Chronic diffuse lesions lead eventually to the development of acidosis, which if not treated will progress to such an extent as to produce the clinical picture of air hunger. In the stage of uræmia acidosis sometimes constitutes the immediate cause of death. In the selection of carbonates for therapy, the bicarbonate meets the essential requirements. The administration of the normal sodium carbonate is regarded as unnecessary and inadvisable. In any acidosis the administration of bicarbonate may be continued until the urine becomes alkaline, even though extensive renal lesions are present.

In the nephropathies which show an increase in tolerance to sodium bicarbonate this salt fails to be excreted, not on account of defective elimination by the kidney, but because there is a deficit of carbonates in the body. When the content of the body has been restored to normal, excretion of bicarbonate takes place and the urine becomes alkaline in reaction.

One of the principal points in this paper is that an acidosis of high grade may occur in the absence of any disturbance in the carbohydrate metabolism and without producing an increase in the excretion of ammonia. Important confirmation of this would be obtained if one could establish an experimental method for the production of acidosis without increasing the output of ammonia. It would also be helpful to know the effect of general anaesthesia upon renal patients in whom the respiratory mechanism is already overtaxed by an acidosis.

If one distinguishes between a disorder of metabolism and an intoxication, then the spontaneous acidoses should be classed as a disorder of metabolism and the term "acidosis" is perhaps more appropriate than "acid intoxication."

This investigation has been conducted in the clinic of Prof. L. F. Barker; it is a pleasure to express my appreciation to him for a stimulating interest in this work.

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THE WORK OF THE OUT-PATIENT DEPARTMENT OF THE HENRY PHIPPS PSYCHIATRIC CLINIC.*

By C. MACFIE CAMPBELL, M. D.,

Associate in Psychiatry, The Johns Hopkins University.

The number of patients registered in the dispensary of the Henry Phipps Psychiatric Clinic since its opening on May 1, 1913, is 543. These patients presented symptoms of mental disorder varying in type and degree. In view of the fact that here is a rather vague idea in the profession at large as to the concrete problems dealt with in such a dispensary, a few preliminary remarks may be excused.

Mental disorder means a disorder of the biological activity of the individual which is shown in its higher adjustments; such a disorder cannot be understood without taking into consideration the complex activities of the individual, not only the chemical, the metabolic and physiological adjustments, but those still more complex adjustments which cannot be adequately described under terms that do not include the concept of behavior. The more complex adjustments, however, may be interfered with by processes which act at various levels of the patient's activity; thus gross damage to the brain by injury may result in very peculiar conduct, or the adjustment to the environment may be interfered with by the acute or chronic action of poison introduced from without, such as alcohol or lead, or developed within the organism, as in pneumonia or typhoid. Or the source of the disorder may lie in alterations in the secretions of the ductless glands, or again the disorder of adjustment may be the result of such changes of the brain as are caused by arteriosclerosis or the senile alterations. Clinical experience, however, forces one to recognize many disorders of adjustment in which no primary disorder at any of these levels can be demonstrated, but where, from more complex causes, the mood of the patient is altered or the general activity changed in type or in quality, or where the patient tries to adjust himself to the environment by subtly transforming his own conception of that environment, leading to those symptoms which the observer describes as delusions and hallucinations. In the evolution of these latter disorders of conduct, the difficulties inherent in the individual present as a rule the most important problem, but the exact test presented to him by the environment and the amount of strain which this puts on the individual's power of adaptation must never be ignored, and sometimes is the important factor open to modification.

The above remarks may show how necessary it is in dealing with a case of mental disorder to keep in mind the possibility of a primary disturbance at various levels of the patient's activity. The physician must make sure that the simpler mechanisms are intact before he inculcates the more elaborate mechanisms. An adequate physical examination is, therefore, the basis of any satisfactory psychiatric examination. An examination of a mental case is thus rather complicated and can ignore none of the usual clinical methods of examination in the presence of any indications for its use. The time demanded, therefore, in psychiatric work is considerable. In dispensary work time is limited, compromise is inevitable, and therefore the physician goes directly to those factors which experience leads him to consider the crucial factors in the individual case. This does not indicate a tendency to undervalue the rôle played by the simpler mechanisms in some types of mental disorder. It simply means that in certain cases experience has led the physician to lay most stress on the complex activities of the individual, and that it is in this sphere that he expects to find the factors which are open to modification.

To give as concrete as possible a picture of the actual work done in the dispensary, I should like to make a very summary review of 50 consecutive patients who were treated in the month of January. Of these 50 patients, 13 were children, 7 were adults with marked constitutional mental defects, 16 presented symptoms either of a recognized type of psychoneurosis or of a less well-defined invalidism, 4 were cases of dementia præcox, 5 had organic brain disorder, one had manic-depressive insanity, one patient was an epileptic, 2 were unclassified on the ground of insufficient data for diagnosis, chiefly on account of difficulty of language; in one case the symptoms did not go beyond the limits of a normal depression.

With regard to the cases of organic brain disease, 3 of these patients were taken into the clinic for further study and treatment. The cases of dementia præcox and of manic-depressive insanity were brought to the dispensary for the purpose of diagnosis and an outline of treatment.

The 13 children might be divided into 4 groups:

1. Children so seriously backward in their school progress as to be recognized as abnormal.
2. Children presenting marked defect of character accompanied by pronounced intellectual defect.

*Read at a meeting of the Baltimore City Medical Society, Feb. 3, 1914.

3. Children with psychoneurotic symptoms.

4. Children with pronounced speech defect.

With regard to the children with simple intellectual defect, the degree has always been estimated by the Binet-Simon scale. The etiological factors have been gone into and an attempt made to find out how far the defect could be attributed to ante-natal conditions, or to some organic lesion, either at childbirth, or during some infectious disorder of childhood. The family history of some cases has been investigated in a detailed manner by a special worker. The practical question with regard to such children is the extent of the further possible development in the individual case. Is the defect based on any remediable cause, is it only an apparent defect? Thus a child with a refractive error uncorrected, with headache, unable to maintain sustained attention, may fidget, annoy the others, become a source of annoyance to the teacher, get quite out of touch with the authorities, drift into the company of the really bad boys and develop habits impossible later to eradicate. Can the child be expected to become a wage-earning citizen and should its training have that in view, that is, should its training be along the lines of teaching in the ordinary grades, assuming that the ordinary school curriculum is a reasonable one? Or is the child never going to be a self-supporting social unit, will it always have to be safeguarded against exploitation, against becoming the tool of the unscrupulous, against becoming a disseminator of immorality?

Children with marked mental defect not based on remediable conditions require special training. The aim of this training should be correct conduct and the acquisition of mechanical ability, and not the general concepts of ordinary education. When the constitutional defect is not definitely recognized, the teacher is apt to apply misdirected energy, *e. g.*, to try to teach a boy of 8 or 9 years something which, with his defective equipment equal to that of a boy of 4 or 5 years, he is absolutely unable to grasp. Such children waterlog a class, impede the teaching of the more valuable scholars without conferring any compensatory advantage on the defective child. It is, therefore, important that the child should to a certain extent be standardized and his education have a direct reference to his actual capabilities. A satisfactory training of the child is the best guarantee of the later happiness of the individual. Unless the defect is recognized and proper measures taken, the child is apt to drift into bad company, develop criminal habits, and be a serious draw-back to the community. The danger of the exploitation of the female is obvious.

In many children, the general mental defect is accompanied by a variety of neurotic symptoms, and these children present extremely interesting problems. The psychoneuroses in the adult are only intelligible in the light of the development of the character of the individual, and in the children with neurotic symptoms one has the opportunity of studying at a very early stage developments which throw much light on the disorders of the adult.

The children are difficult to study under dispensary conditions. At first they are shy, uncommunicative, on the defense. Their visits are apt to be at rather long intervals, they are in a peculiar environment which does not elicit their character-

istic reactions. Therefore one is frequently almost altogether dependent on the anamnesis. Here the social service department is able to give invaluable aid and to furnish a good idea of the actual environment of the child and of the remediable defects which it presents.

The following cases illustrate types of children dealt with:

Jan. 9, 1914. E. C. D., a boy of 7, is getting along very well at school, but during the last year has presented evidence of unstable equilibrium. The boy has bad dreams, and he has recently been stealing. The aunt considers that these symptoms came on after an operation for hernia last year, but the boy already had some difficulty with his instinctive life even before that. He had already been masturbating for about one year and he wet the bed until the age of six.

Remarks.—The case illustrates the frequent occurrence of fears and bad dreams in association with difficulties in the sexual life. It shows the importance of these fears as evidence of the advisability of helping the child in the sphere where help is apt to be refused. Scolding and punishment are apt merely to increase the tendency of the children to deal in a blind and evasive way with troubles which are almost inevitable in the course of development. The relation of stealing to the other difficulties of the patient has not been traced, but it is a symptom which must not be accepted as an irreducible defect of character, but as something which may be further analyzed and modified. It may be possible to help this boy by some educative talks and thus prevent the further development of an evasive way of dealing with his personal difficulties.

Jan. 17, 1914. A. A., a boy of 8½ years, had been pilfering for four or five months. The father dragged the boy to the clinic on the chance that the doctors might remove something from the boy's brain. At the consultation the boy was absolutely uncommunicative and frank relationships were not established. The father, disappointed at the impossibility of an operation, did not think it worth while to bring the boy back to the clinic. The social service worker made a home visit. She found that after each episode of pilfering, the boy was not punished physically, but was threatened and scolded to such purpose that for two or three days he was panic-stricken and in tears. The case presents a problem of very great importance, and the endeavor will be made to try and get into friendly relationship with the boy to see whether the stealing can be understood more clearly.

Jan. 9, 1914. C. E. D., a boy of 9½, whose mental age is 7½ years. The mental retardation is here due not to faulty environment or to a poor education, but to actual disease of the nervous system. The boy was a seven months child, had spasms at 18 months, frequent screaming spells until 5 years, and later, occasional attacks of a convulsive nature.

Remarks.—This case is one of a very large group of children who are brought to the dispensary, with a history of convulsive phenomena at some period of childhood. In some cases the disorder is in relation to more or less coarse damage to the brain, which appears to have been caused either by prenatal influences, difficulties of child-birth, or infective disorders in infancy. In other cases the patient presents no neurological symptoms except the convulsions, and the etiological factors are very obscure. From the point of view of treatment, these patients are of course very disappointing. They form an interesting material of study, for our knowledge of convulsive phenomena and the underlying conditions is extremely meagre.

Jan. 12, 1914. J. B., a boy of 14, during the winter of 1912-1913 began to stay in the house and made only desultory attempts to play or read. He showed a marked change of disposition and was quarrelsome with the other children. He would sit about in the house, fidgeting in his chair, smiling without cause. He became careless in his dress and as to personal cleanliness. At the same time he showed a compensatory fastidiousness with regard to eating. He would wash his dishes over and over before eating. He would refuse to eat things, saying that they were not clean. He was easily frightened, especially at night.

Remarks.—The case is evidently a rather serious one. The symptoms have no doubt to be partly understood in relation to the habit of masturbation, which had been learned from association with a gang of bad boys. The father spoke freely to the boy about it, but as a matter of fact the boy is rather afraid of his father.

Two cases may be referred to who have been coming to the dispensary for a considerable time:

May 24, 1913. M. S. is a queer, jerky little girl of 7 who is extremely fidgety, jumps about the room in a somewhat odd manner, is at times inattentive, asks questions as if she were rather stupid, and is apt to pretend that she does not know the nature of the place, the occupation of the doctor, etc. What is especially characteristic of this patient is her incessant asking of questions, many of which have quite obvious answers. Although the patient makes a superficial impression of being stupid, she is of normal intellectual level and her teacher finds her quite bright at school.

Remarks.—To understand the underlying forces and the mechanism of such a disorder is a difficult and tedious task, and is not made any easier by the infrequency of the visits to the dispensary. It is important to take this eager questioning of the child seriously, and to find out what are the main questions and what is the curiosity which thus expresses itself so indirectly. In this case the social service worker has visited the home regularly for a period of three months, and has been fortunate in establishing a very frank relationship. She has enabled the physician to understand the repressive atmosphere in which this child has been brought up and which put a strict taboo on many of the simple questions of the child. The mother expressed doubt to the social service worker as to whether she had done right in omitting to punish her 2½-year-old child, who had made some reference to his sister being in the toilet. The father was disturbed at the possibility of the patient being taught folk dances. "Is it necessary to ruin her soul in order to save her body?" The social worker has done what was possible in the way of advising the parents in matters of training and in the regulation of the habits of the child. She also conferred with the school teacher. The child was also taken into the Harriet Lane Home for a short period of observation.

May 21, 1913. W. S., a difficult boy of 12½ years, inattentive at school, unruly and bad-tempered at home, destructive and fond of teasing animals and children. The environment, however, was probably partly the cause of the boy's difficulties. The father punished the boy severely for every misdemeanor. After school hours he was obliged to study Hebrew with his father and had little time for amusement. The mental age of the boy was that of a child of 11 years. In school he was often punished, and on this account he disliked his teacher.

Remarks.—In this case a careful review of the whole situation with the parents was of great benefit and the boy reports

to the dispensary regularly. The social service worker has obtained the intelligent cooperation of the family in the carrying out of the doctor's instructions as to a consistent home training. She has held monthly conferences with the school teacher whose latest report is that the patient's progress and general attitude are excellent. The boy has been brought into touch with a boy's club and gymnasium, where he is doing good work.

The social service department has also done a great deal for W. B., a boy of 11, who reports regularly at the dispensary. For some years he has shown choreiform movements. He is rather erratic in his behavior, fastidious in his food, disturbed in his sleep, afraid to sleep away from his parents. The boy was taught masturbation by comrades and treated improperly by an adult. For this latter episode he received a thrashing from his grandmother, which probably was the extent of the child's education as to how to deal with one of the most fundamental factors in his life. The combination of the symptoms in this case is a very common one, sleeplessness, disturbing dreams, fears, bed-wetting, masturbation.

Remarks.—In this case obviously the whole education of the child was at fault. The capriciousness of the child's eating and the irregularity of his hours were merely partial expressions of the result of a thoroughly faulty education. To deal with such a situation an efficient social service department is absolutely necessary. The worker has visited the family regularly, has instructed the parents in detail as to hygiene, has secured dental care for the patient, has given him a vacation in the country, has arranged for his admittance to the ungraded class and has talked with the principal and teacher as to his special needs.

Sixteen cases were grouped together, which presented either recognized types of psychoneurosis such as hysteria, or rather vague and ill-defined types of invalidism. It is not easy under dispensary conditions to do justice to such patients. The treatment involves the re-education of the patient, a tedious and difficult task.

The following cases may illustrate the problems presented by this group of patients:

Jan. 22, 1914. S. B., a young woman of 26, for several years had complained of a variety of symptoms, headache, hot flushes, burning sensations in her stomach, dizziness, sleeplessness, occasional nausea and vomiting. Apart from these symptoms, she said that she was quite happy, in fact the happiest woman on earth; this, notwithstanding the fact, later admitted, that she did not love her husband and still hankered after an old sweetheart whom she had discarded four years previously. The patient had been treated for several months. At first the symptoms were attributed to a hypothetical hyperthyroidism, but later it was concluded that all the symptoms were of psychogenic origin.

Remarks.—In such a case it is possible to let the patient understand much more clearly the relation of the symptoms to the underlying difficulties in her life. One still, however, has to face the unfortunate situation which the patient has created by marrying her husband on grounds of prudence, where her feelings were altogether with another man. Such a situation is a very important factor in perpetuating psychoneurotic symptoms once they are established.

Jan. 17, 1914. N. E. H., a young woman of 23, had recently passed through a brief semi-delirious episode, but now presented

only a vague nervousness with surface cheerfulness and conventional smile. In this case, too, the problem was to educate the patient in regard to those factors which had been dealt with very evasively, the semi-delirious episode itself being the disguised expression of factors repressed from her conscious life.

Jan. 28, 1914. B. K. M., a clergyman of 46, several months previously had had an attack of quasi-unconsciousness, since when he had complained of excessive fatigue. Nineteen years previously he had had a nervous attack which his physicians said bordered on St. Vitus' Dance. The very fact that he had become a clergyman was to a certain extent a compensation for difficulties not squarely met. He had given up another occupation to enter the ministry, and one year later he had the involuntary movements referred to above. In the third year of the ministry he had a worse break-down. Nine years later he had an attack of shortness of breath, palpitation, marked anxiety, disturbing dreams of the nature of nightmare.

Remarks.—Even in a single interview it was possible to see in outline the mechanism of the disorder, and to put this before the patient. The amount of insight thus acquired by the patient along with the reassurances given him seemed to be decidedly helpful. Such a case, however, requires rather prolonged treatment, and the patient did not live in Baltimore. The case was gone over with the family physician who accompanied him, and the patient was recommended to go over with his physician in very much greater detail the main points which had been only partly reviewed during the consultation.

The following cases represent a type very familiar in dispensary work, so familiar as to have lost much of its interest for many physicians. Although familiar with these cases, we are, however, far from understanding them and they present problems of very great psychiatric interest.

Jan. 20, 1914. H. G. is a very typical example of this group of patients. She is a woman of 39, very unhappily married, who says that she is tortured by her husband, that he makes her sick, that she only wishes to live for her children. The patient complains of a variety of somatic symptoms, pain in the head, tightness in the chest, pain in the abdomen, but a thorough physical examination reveals nothing to account for her bodily symptoms.

Remarks.—The patient's invalidism appeared to be in close relation to her general unhappy situation. She had, however, not reacted with the special symptoms of a hysteria nor another psychoneurosis. This type of invalidism is partly intelligible as a reaction to the definite situation; to a certain extent it affords protection from the demands of the environment and brings in certain immunities and privileges. It might best be described as a "situation-neurosis." The importance of the formulation in this term is that we keep before us the practical problem of seeing whether after all the situation may not be advantageously modified, so that we do not confine our-

selves absolutely to dealing with the patient as an isolated unit. At the same time it is important to encourage the patient to face frankly the difficulties of the situation and to realize the presence of internal obstacles of which she was previously ignorant. We thus try to improve the adjustment of the patient at whatever point we find available for modification. It is probable that in this case the patient had never in her life reached a satisfactory level of independent activity. As a child she had been wrapped up in her mother, and after the death of her mother she said that she had cried a whole year. The analysis of the development of her character and of the circumstances which led to her unsatisfactory marriage would probably have thrown some light on the later development of invalidism, which after all represented a rather childish type of reaction.

Jan. 27, 1914. A. A., a Hebrew woman of 38, complained fluently and continuously of innumerable pains. She clamored for sympathy. She knew that the hospital doctors could not help her, but she could not stay away from them. Whenever she was taken into a hospital, her condition changed entirely and she was well in a couple of days, but she relapsed after her discharge. In this case the same problems are brought up as in the previous one.

Jan. 16, 1914. J. B., a woman of 40, after some trouble with her neighbors, became nervous, sleepless and suffered from headaches. Her complaints found little sympathy with her husband who had been nagging her ever since her marriage 17 years ago. She had been in one hospital, but left after one week, as she was disgusted with the treatment.

Remarks.—In this case we see how an illiterate woman, unhappy with her husband, in the face of additional difficulties in life, falls back on a variety of mild complaints which relieve her of some of her responsibility and throw it on society. It is very difficult in an illiterate patient of this type to do much in the way of getting her to understand the true nature of the trouble, as an inferior adaptation to the actual situation. It is difficult enough with an educated woman of the same age.

It is interesting to notice the percentage of Russian Hebrews in this group. This type of disorder is probably closely related to the racial character and to the special difficulties in the life of immigrants of this class.

The above very summary review may serve to indicate the actual problems dealt with in the dispensary; these problems are not only of great psychiatric interest, but touch many vital interests of the community. They raise important social and educational issues, and it is hoped that even where in the individual case little can be done, the thorough study of the disorder in its complete setting may contribute data of value in relation to the mental hygiene of the community.

DYSTROPHIA EPITHELIALIS CORNEÆ: REPORT OF A CASE.*

By LLOYD B. WHITHAM, M. D.,

Assistant in Ophthalmology, The Johns Hopkins University.

The patient, a negro, 53 years of age, married, and a washer by occupation, came to the clinic on June 9, 1913, com-

*From the clinic of Dr. Samuel Theobald, Baltimore Eye, Ear and Throat Hospital.

plaining that, for several weeks prior to that date, there had been a gradual diminution in the vision of his right eye, unaccompanied by pain. There seemed to be a "shadow" before his eye, and for the past week it had been slightly sore.

Previous medical history negative; no malaria, no trauma, no syphilis. Gross inspection revealed a well-nourished, vigorous man with a rather dry, coarse skin, and a coated tongue, but, on the whole, presenting no abnormal appearance.

Minute inspection of the cornea of the right eye, with the binocular loupe, showed a small, central, superficial, herpetic, epithelial loss, which was clear, uninfiltated, and stained faintly with fluorescein. Midway between the center of the cornea and the limbus a very faint, whitish crescent was seen, evidently lying between the epithelium and Bowman's membrane, or in the anterior lamellæ of the substantia propria. The corneal epithelium, itself, surrounding this area and extending to within about 3 mm. of the limbus, was diffusely clouded and hazy, as though œdematous, minute distinct vesicles being present. There was only slight congestion of the ciliary vessels and the iris was normal in appearance, although the pupillary reactions were sluggish. The tension of the globe was not elevated, and the anterior chamber was not shallowed. No view of the fundus could be obtained with the ophthalmoscope, and vision was limited to counting fingers at 40 cm.

The observer's first thought was of a rare, ring-shaped keratitis, which was somewhat borne out by the fact that the crescent later completely encircled the center of the cornea. However the inflammatory evidences, excluding the vague pericorneal congestion, were so slight, and so out of proportion to the corneal disturbances, that one felt inclined to abandon the diagnosis of an actual keratitis and look upon the condition as a trophic or nutritional affection, an epithelial dystrophy, due, perhaps, to some general dyscrasia, a view which was partially substantiated by finding diminished sensibility of that cornea as compared with its fellow, both being hypo-normal in that respect.

The patient was advised to enter the hospital, and the following examinations were made by Dr. Guerinet:

Neurological and physical—negative.

Blood: Pale, slowly coagulable, little fibrin, Hb. 68%, R. B. C. 3,650,000, W. B. C. 6200.

Differential count: Small mononuclears 24%, large mononuclears 4%, polymorphonuclears 70%, eosinophiles 2%.

Blood pressure, 148 mm.

Tuberculin test (von Pirquet), negative.

Wassermann blood test, negative.

The patient was placed under an appropriate local and general regimen with no appreciable change in the corneal condition, until June 24, when urinalysis showed a specific gravity of 1030, and 0.5% sugar. A strict "sugar free" diet was at once ordered; in six days there was a complete restoration of the corneal epithelium, and on June 30 the patient was discharged and told to report at regular intervals for treatment in the dispensary.

He failed to do so, however, and did not come back until August 18 when he returned to the clinic with the haziness of the cornea much deeper, more diffusely located, and amounting to a positive stippling—giving the epithelium a roughened appearance, as of glass which had been breathed upon.

It is interesting to note, in this connection, that on an intervening and unrecorded occasion, the man returned to the dispensary with a foreign body impacted upon the diseased cornea. My colleague, who was in charge at the time, upon brushing off the particle with a cotton-wound spud, noticed that the hazy epithelium at that situation was wiped away also, leaving clear substantia propria beneath. This demonstrates how superficial was the œdema.

Upon his return, in addition to an increase in the œdema, there was a large, central, bullous loss of epithelium, deeper than the first, and staining markedly with fluorescein. The whitish ring was more pronounced.

He was promptly re-admitted, and again placed upon a rigid sugar free diet, close questioning having revealed the fact that he had been partaking freely and indiscriminately of starch-contain-

ing foods. The same local and general treatment was ordered as on the previous visit.

On this occasion a slight transitory hypertony was several times noticed, although ophthalmo-tonometry was not resorted to, because of the epithelial disturbances. In fact, the epithelium did not respond to therapeutic and dietetic measures as rapidly as before, and complete restoration did not occur for 18 days. This time the patient complained, once or twice, of slight local pain, which was promptly relieved by instillations of a 1% holocain hydrochlorid solution.

On September 8 he was again discharged from the hospital with the corneal haziness much less marked, while a very dim, undetailed view of the fundus could, for the first time, be obtained with the ophthalmoscope. His vision, 4/100, also showed great improvement. Urinalysis gave a high specific gravity—1031, but no sugar, acetone, or diacetic acid. In this connection, let it be noted that, while the diet caused a loss of weight, and less healthy general appearance, the corneal disturbance was steadily ameliorated thereby.

He was next seen on October 10, when his vision had improved to 20/120, and the œdematous haze of the cornea had cleared markedly. The iris was clearly visible, but the white ring was still present, while the corneal apex was marked by a small, almost circular, opaque spot, the site of the previous tissue loss.

Four days later, however, when he brought a 24-hour specimen of urine to Dr. Guerinet, 2% sugar was found, in conjunction with a specific gravity of 1032, although there were no decomposition products such as acetone or diacetic acid.

Strict dietary instructions were again given him, and he was told to instil 5% dionin collyrium locally, each day, in order to stimulate the nutrition of the cornea.

The man was last observed on October 31 when the cloudiness had diminished greatly, but below the corneal center, and above the white ring, a small bulla had formed, evidently containing a clear liquid. This was directly beneath the epithelium and moved in any direction when pressure was made against it through the lower lid. Vision had fallen slightly, being 20/160 ++, although a 2.25 diopter convex sphere, tried for the first time, brought it to 20/50.

In a rather careful survey of the literature upon the subject of corneal dystrophies, the writer has been unable to discover a single reported case with diabetes as either the exciting or indirect cause. In fact, those who have reported the condition, Fuchs, Paul Knapp, Troncoso and Reese, have consistently failed to detect any definite ætiological factor whatever. They agree, however, in almost all of the following points: that dystrophia epithelialis corneæ occurs most frequently in middle life, that it usually affects the female sex, with a predisposition for the right eye, that it is frequently associated with slight and transitory rises in the intraocular tension, and, finally, that the course of the degeneration, as well as the visual diminution, is gradually progressive, despite any known form of treatment.

The condition, as such, was unknown until 1910, when Fuchs' interesting monograph appeared, describing the 13 cases he had seen since 1900. As he says, many cases, prior to that time, had undoubtedly been diagnosed and treated as glaucoma, owing to the elevation of intraocular tension, and the almost characteristic appearance of the corneal epithelium. Since his splendid description of the course and character of the condition, however, several observers have diagnosed

similar cases, and added their reports to the literature upon the subject, a total of 17 cases.

The slow and progressive course of this condition distinguishes it clinically from any of the inflammations, for the latter are marked by a period of progression, followed later by one of regression, while anatomically the dystrophies are characterized by degenerative changes as opposed to the cellular invasion of inflammatory lesions.

The majority of dystrophies are the expression, either of a local disturbance of nutrition, or, as Reese has pointed out, some general malnutrition; for example: the deposits of mucin in myxœdematous subjects after thyroidectomy, the grayish-green discoloration of the cornea occurring in disseminated sclerosis, and, according to Weeks, disease of the Gasserian ganglion and traumatism. (A physiological parallel to the dystrophies is found in the familiar "arcus senilis.") But, to dystrophy of the corneal epithelium no definite ætiological factor has been ascribed. Hence the writer feels some hesitancy in advancing his opinion that diabetes was the direct or remote cause in the case which has just been reported, even though the diet and presence or absence of sugar did so markedly influence the ocular condition.

If the metabolic disease in question did bear some definite relation to the trophic disturbances which took place in the cornea, some interesting conjectures as to the *modus operandi* might be made. Was the process caused by a direct toxic action on the trophic apparatus, for instance, by a temporary flooding of the blood or lymph with diacetic acid or beta-oxybutyric acid? Or was the degeneration purely a nutritive one caused by a perversion of the pabulum normally carried to the corneal epithelium, and due to a degeneration in the walls of

the small blood vessels? Again, might the bullous condition of the epithelium be analogous to the desquamative dermatitis so constantly observed in diabetes?

Epithelial dystrophy is easily differentiated from Family Nodular Keratitis, from affections due to noxious vapors, from keratitis vasculosa with herpes, from post-operative sclerosis, and from hyaline or fatty degeneration of the cornea.

The case just reported resembled those of Fuchs in that it was associated with transitory periods of hypertony, and, somewhat one described by Reese with a bulla in the center of the opaque cornea. It makes the third reported case associated with pericorneal injection.

The pathology of dystrophia epithelialis corneæ is rather vague: Paul Knapp contends that it is due to an œdema of the epithelium. Fuchs has had the opportunity of making a microscopical examination of one case. There was grayish opacity and roughening of the surface of the cornea from small vacuoles in the epithelial cells, and *newly formed tissue between Bowman's membrane and the epithelium*. This tissue is homogeneous, and without signs of hyaline or mucoid degeneration. The epithelium covering it is thinner than normal, but the cells are not flattened or hornified. He thinks that in the earlier stages the epithelium is probably thickened and vacuolated.

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LOUIS HÉBERT.*

By M. CHARLTON,

Librarian of McGill Medical Library, Montreal, Canada.

Every student of Canadian history knows that from the first days of the colonization of New France, an important rôle as colonists was played by members of the medical profession. If they were not remarkable for any great professional brilliancy, they were generally men of sterling character and courage. Louis Hébert, apothecary, surgeon, and agriculturist, is regarded, next to Champlain, as the "Father of New France." When Champlain induced his old friend of Port Royal to venture once more to become a colonist of New France, he knew he had accomplished a greater work in building up his colony than had been done since its foundation. For Louis Hébert had proved his worth at Port Royal, not only as a surgeon, but as a keen and ardent agriculturist.

When Champlain returned to France in 1617, his mind filled with the wondrous future he was planning for Quebec, he knew it was of vital import to obtain as colonists men of the best type, not jail-birds, as Roberval had had to contend

with, nor mere adventurers, who came for the love of adventure or gain, and went away again, but men who would cultivate the land. And so the thought of his friend came to him—Louis Hébert, who had cultivated such beautiful gardens at Port Royal, until that settlement was destroyed by Samuel Argall, when Hébert returned to France.

Louis Hébert had received a good education, for his father was a man of repute, being apothecary to Catherine de Médicis. Louis followed his father's business and had a shop on the banks of the Seine, where he was well patronized. But in the summer of 1606, he suddenly announced to his friends and relations that he was sailing with Poutrincourt and fifty other colonists for the New World, of which there had lately been so much talk. Among others who sailed in the ship was a Parisian lawyer, historian, and poet named Lescarbot, the friend and lawyer of Poutrincourt. It is to Lescarbot we are indebted for the vivid portrayal of how the first winter in the new settlement at Port Royal was passed. "For my part," writes Lescarbot, "I can say that I never worked so hard in

* Presented by Dr. Henry M. Hurd at the meeting of The Johns Hopkins Historical Society, March 9, 1914.

my life. I took pleasure in laying out and cultivating my gardens, in making alleys, building summer houses, growing wheat, rye, barley, oats, beans, peas, and garden plants, and in watering them, for I was most anxious to find out, by personal experience, the quality of the soil."

With Lescarbot worked Hébert and the days were not long enough for these two enthusiastic agriculturists; they must needs work by moonlight, digging and planting. Lescarbot and Hébert returned to Paris in the autumn of 1607, but Hébert, after a short stay, came back to Port Royal accompanied by Biencourt, Poutrincourt's son. He assisted Biencourt in managing and taking care of those colonists who had remained, and when Biencourt was absent, acted as his lieutenant until the place was destroyed in 1613, by the English. Hébert then returned to Paris as he thought, for good, and once more opened his shop on the banks of the Seine.

When Champlain arrived in France in 1617, he visited Hébert, and so beguiled him with his marvellous accounts of the country about Quebec that Hébert again sold his possessions and with his family started for Honfleur, where he arrived on March 14. Champlain had induced a new fur trading company to promise to support Hébert and his family for two years, and afterwards to make him an allowance of two hundred crowns for three years.

On arriving at Honfleur, Hébert found, to his chagrin and dismay, that all the promises which the company had held out to him were false. In vain did Hébert appeal for fair treatment. The company refused to keep their promises; they offered him one hundred crowns instead of two hundred, and, moreover, required his bond for free medical attendance at all times to the settlers and to the clerks belonging to their company. Hébert was at their mercy, but rather than return to Paris, for he had disposed of all his effects, he embarked with his family for the New World.

Their passage was a stormy one, and when they reached Newfoundland, the ship encountered a great field of ice-bergs. At one time, it seemed as if all on board must perish. Father Joseph, one of the passengers, knelt upon the deck and prayed for Divine assistance, and we are told in the "Relations of the Jesuits" that Madame Hébert took Marie Rollet, her youngest child, and held her up through the hatchway, so that she might receive the father's blessing. It was on this long and stormy voyage of thirteen weeks and a day that the courtship of Anne, the eldest daughter of Hébert, commenced. Among the passengers was one Etienne Jonquest, a sturdy son of Normandy. He wooed Anne so successfully that the two were married in the autumn by Father le Caron. This was the first marriage in Canada according to Church rites, but Anne had a short married life, for she died in 1619 and was followed by her husband within a few weeks.*

*Thus we have mention of the first marriage in New France, and in connection with that it is interesting to notice the first marriage in New England took place the 12th of May, 1617, ten months and a half earlier, between Edward Winslow and Sarah White.

The passengers were first landed at Tadousac June 14, and after returning thanks for their safe arrival, they went on to Quebec.

Quebec consisted at this time of a few roughly-built huts, clustered close to the water's edge; they were inhabited by clerks, interpreters, and others employed by the company.

Louis Hébert chose for the site of his future home, land on the height above—later called Mountain Hill, part of which was between the present streets of Famille and Couillard. He lost no time in building his home, a substantial stone house, thirty-eight feet in length by nineteen in width, the best house for many years to come in Quebec, and the first dwelling in what was afterwards the Upper Town, for as yet Champlain had not built his fort on the cliff. Not far from the house ran a stream of pure water, and this had decided Hébert in his choice of a site. For ten years Hébert toiled like any hardy peasant upon his farm. He sowed Indian corn and vegetable seeds, planted apple trees and his beloved grape vines. All his spare time, when not attending to the sick, was devoted to his agricultural pursuits. Every year he cleared more ground and tried fresh experiments in farming; every year his farm grew more and more productive. He was able, almost from the first, to support his family on what he raised, and this in spite of the fact that the company forced him to sell them his grain at a price fixed by themselves, one of the many acts of injustice rendered him by the company. This farm was the show farm of Quebec—the model farm, so to speak, of the day. From this time agriculture began to find its place in New France, and in these golden days of Canada's greatness, she may well be proud of her first farmer.

It is claimed that the first seignory mentioned in the records was that of Sault-au-Matelot near Quebec, which was ceded to Louis Hébert by the duc de Montmorency in 1623 and that this was added to three years later by the duc de Ventadour of the fief of d'Epinay on the St. Charles River. A controversy has arisen, however, as to whether Hébert may be rightly called the first seigneur in New France.

The life of this clever, original Frenchman was crowded with interest, from the day he first left Paris and settled at Port Royal to his final home at Quebec. Through innumerable hardships and difficulties he had struggled on with unfailing courage and hope. He had accomplished wonders during his ten years' residence at Quebec. In January, 1627, a great sorrow came upon his friends. Hébert fell on the ice when he was crossing a river and died shortly afterwards from the effects of the fall. They buried him amidst great grief in the cemetery of the Recollet Fathers at the foot of the cross. Only three days before his accident, Hébert had visited the Fathers and as though he had had a premonition of his death, he had requested that when that event took place, he should be buried in that spot.

It is supposed that the first time a notary's services were required in New France was in the drawing up of Hébert's will.

Among the settlers who had remained at the advice of

Champlain, when Kirke captured Quebec, were the Hébert and Couillard families, as well as a surgeon, Adrien Duchesne and his wife, who came to Quebec in 1618. Duchesne was the second medical man to settle there.

When Champlain returned to Quebec after the treaty of St. Germain-en-Laye, he was accompanied by Fathers Paul le Jeune and Anne de la Nouë. They went immediately to Madame Hébert's house, the only one spared in that scene

of desolation. Here Madame Hébert lived with her second daughter, Guillemette and her son-in-law, Guillaume Couillard. Couillard had come to Quebec in 1613 as a carpenter. But he had soon become, under Louis Hébert's teaching, an active farmer. In 1628, instead of tilling the ground by hand oxen were used, and so well had Couillard managed Hébert's farm that it was spoken of as the one fertile spot at Quebec when Champlain returned.

PROCEEDINGS OF SOCIETIES.

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY.

December 15, 1913.

A Case of Infection with *Agchylostoma duodenale* Treated with Oil of Chenopodium (with Demonstration of Specimens).

DR. ROBERT L. LEVY.

The patient, a Norwegian sailor, aged 23, was admitted to the Johns Hopkins Hospital eight weeks ago, complaining of headache, general bodily pains and swelling of his legs. He had always been strong and a hard worker, and had sailed to almost all parts of the civilized world. The present illness began in Mexico one month before admission here. There, for the first time in the course of his wanderings, he went about barefoot. He soon developed a painful sore on the dorsum of the left foot, which discharged and resisted all efforts made to heal it. He noticed no itching of the foot. Shortly afterward the feet and legs began to swell and the patient felt weak, irritable and incapable of work. He went to a hospital in Mexico and remained there three weeks; during this time he was given no medicine. The swelling of his legs, however, disappeared and he was discharged somewhat improved. Twelve days before admission here his legs again began to swell, he felt feverish and weak, and there was moderate diarrhoea, so he boarded a ship for this country and landed in Baltimore.

On admission there was striking pallor, fever, tachycardia, brawny oedema of ankles and lower legs and a pigmented scar on the dorsum of the left foot. He was extremely weak and very irritable. The blood showed 1,660,000 red cells, 6,440 white cells and a hæmoglobin of 25% (Sahli). In addition, there were seen many hyaline and crescent forms of æstivo-autumnal malaria. An examination of the stools revealed the ova of *Trichuris trichiura* and of the hookworm.

The malarial infection was soon gotten under control. The whip worm ova spontaneously disappeared from the stools following vigorous purgation, but the usual medication with thymol, as recommended by the Porto Rican Commission, failed to get rid of the uncinaria, though thrice repeated at one week intervals.

Accordingly, our patient was given the oil of chenopodium according to the directions (slightly modified) of Schüffner and Verwoort (München. med. Wchnschr., 1913, LX, 129). The patient was starved for eight hours, at the end of which period he was given an ounce of Epsom salts. Two hours later, 16 drops of the oil of chenopodium on a teaspoonful of granulated sugar were administered. This dose was repeated at two-hour interval until three doses had been given. Two hours after the last dose of chenopodium the patient was given an ounce of castor oil and 50 minims of chloroform. On sifting the stools collected during the next 24 hours, 19 hookworms of the Old World type were found. Ova continued to be discharged in the fæces. On repeating the treatment five days later, seven more hookworms were expelled and this time no ova could subsequently be demonstrated in the stools. However, another course of chenopodium was given to be sure that no parasites remained; none were expelled. The stool has since been free from ova, and I believe we may consider the patient cured of his intestinal parasitism. He has gained 30 pounds in weight. The blood now shows:

R. B. C., 4,110,000; W. B. C., 11,000; Hb. (Sahli), 70%. It is of interest that whereas on admission the eosinophiles formed but 7% of the white cells, there is now an eosinophilia of 36%. Such a rise in eosinophile cells the Porto Rican Commission regards as of good prognostic import.

As compared with thymol as a vermifuge in uncinariasis, oil of chenopodium seems to offer certain very definite advantages:

1. According to Schüffner and Verwoort it is more efficacious.
2. It is not unpleasant to take.
3. Its ingestion is not accompanied by any disagreeable after effects. In a recent article Stiles and Boatwright have pointed out that unpleasant symptoms appeared in over half of a large series of cases treated with thymol, and carefully observed to determine this very point.
4. In therapeutic doses it is non-toxic. Thymol occasionally though rarely, produces symptoms of serious intoxication.

NOTES ON NEW BOOKS.

In Memoriam: Dr. James Livingston Thompson. Dr. Daniel A. Thompson. (Indianapolis, Indiana, The Hollenbeck Press, 1913.)

This small volume is a collection of pleasant and fitting tributes to these two noteworthy practitioners of Indianapolis. They were both men of mark; but many fine men like them pass away, and their work and names are soon forgotten, for they are uncommemorated, and so such "In Memoriam" tributes are always precious records in the history of the medical profession. All friends of these two doctors will be grateful to see these warm expressions of affection and esteem thus perpetually recorded.

Surgery of the Upper Abdomen. By JOHN B. DEEVER, M. D., etc. and ASTLEY PASTON COOPER ASHHURST, M. D. Vol. II. Illustrated. \$5. (Philadelphia: P. Blackiston's Son & Co., 1914.)

It is more than four years since the first volume of this excellent surgery appeared, but the wait is compensated for by the thoroughness and completeness of the second and last volume. The authors have carefully studied the great amount of literature on the subjects treated—gall bladder, liver, pancreas and spleen—and their work is one that all surgeons will be glad to own. Their reputation gives weight to their words, and the lists of references make it easy for the reader to look up original articles. The new

Completed "Surgery of the Upper Abdomen" is an important contribution by American authors to the literature of surgery, and will bring them well won repute by foreign students of the subject.

Merck's Annual Report, 1912. Volume XXVI. (Darmstadt, C. Merck, Chemical Works, 1913.)

Pharmacologists especially, and those who teach therapeutics, will find in this volume much valuable information on the newest remedies. The work is reliable, carefully prepared from the best authorities, and is conveniently arranged. The physician, at a loss for some new remedy, can easily secure one for almost any disease and symptom from this list, and can use it with safety. He follows the directions given.

Science and Education: A Series of Volumes for the Promotion of Scientific Research and Educational Progress. Edited by J. McKEEN CATTELL. Volume II. *Medical Research and Education.* By RICHARD M. PEARCE, WILLIAM H. WELCH, W. H. HOWELL, FRANKLIN P. MALL, LEWELLYS F. BARKER, CHARLES S. MINOT, W. B. CANNON, W. T. COUNCILMAN, THEOBALD SMITH, G. N. STEWART, C. M. JACKSON, E. P. LYON, JAMES B. HERRICK, JOHN M. DODSON, C. R. BARDEEN, W. OPHÜLS, S. J. MELTZER, JAMES EWING, W. W. KEEN, HENRY H. DONALDSON, the late C. A. HERTER and the late HENRY P. BOWDITCH. (New York and Garrison, N. Y., The Science Press, 1913.)

The basis of this handsome book of 536 pages seems to be the Hitchcock Lectures delivered at the University of California in 1912 by Prof. R. M. Pearce, of Philadelphia (originally published in *Popular Science Monthly*), which cover 88 pages; the remainder of the book consists wholly of papers published during the past twenty years in various medical and scientific journals. They all represent different strata of thought during the period mentioned and consequently at the present time possess very different values. Some of the issues discussed have passed into history and have given place to new ideas and suggestions which a decade ago would have seemed subversive of proper conceptions of medical education.

The most interesting of Prof. Pearce's lectures relates to problems in immunology, protozoology, chemotherapy, physiological chemistry, experimental pharmacology and experimental pathology, in which he gives an admirable review of the studies in immunity which were initiated by Behring and Kitasato, and later led to the diphtheria antitoxin of Behring and Knorr; the antibacterial sera of Ehrlich; the opsonins of Wright; the practice of immunizing vaccinations as now best illustrated in typhoid fever; the Wasserman test by fixation of complement; the condition of increased susceptibility known as anaphylaxis; the study of filterable or ultramicroscopic viruses by Flexner and their relations to epidemic poliomyelitis.

In protozoology he speaks of the discovery of the first protozoon definitely associated with disease in man in 1860 and known in 1875 to be the cause of amebic dysentery; of the discovery of the *plasmodium malariae* by Laveran in 1880 which settled definitely the cause of malarial fever; of the discovery of the cause of Texas fever in 1893 and its mode of transmission by Smith and Kilbourne, which had important influence subsequently on the study of the transmission of malaria and yellow fever, sleeping sickness and other diseases due to pathogenic protozoa. This admirable review is followed by a review of the wonderful work of Ehrlich in devising a method of combating protozoan diseases by direct toxic agencies to destroy the specific protozoon; and of the discovery of salvarsan to destroy the spirochetes of syphilis. He believes that "with a record of about a dozen drugs which can be used to cure or modify disease caused by nearly a dozen different protozoa, chemotherapy offers promise of results which with

serum therapy and vaccination in bacterial diseases will sharply limit the ravages of the transmissible diseases of man and animals." In the same lecture he traces the growth of physiological chemistry in its investigation of problems of digestion metabolism and secretion in health and disease to ascertain better the mechanism of cell activity and the interrelation of the functions of cells in different parts of the body. His references to experimental pharmacology, experimental pathology and experimental physiology, although much less extended, are full of interest. The whole series of five lectures is of unusual value and should go into the hands of all medical students. They bring into compact form the methods and results of medical research and point out suggestive means of further study.

The succeeding papers as already intimated are of varying interest, but all are valuable contributions to many important branches of medical education. Occasionally, as in Councilman's "Experiences of a Medical Teacher," especially in a conspicuous foot-note on optimism, we get a refreshing vein of characteristic cynicism. The enterprise of the industrious editor of the series is worthy of all praise. It is to be hoped that the succeeding volume on "University Control" may be presented upon a similar plane of high idealism. The whole situation calls for a much less personal attitude than has characterized the majority of writers upon it.

Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India. 1/9. (Calcutta: Superintendent Government Printing, India, 1913.) No. 60 (New Series).

Studies on the Mouth Parts and Sucking Apparatus of the Blood-Sucking Diptera.

No. 4. *The Comparative Anatomy of the Proboscis in the Blood-Sucking Muscidae.* By CAPTAIN F. W. CRAGG, M. D.

For a small class of specialists these reports of Captain Craggs are of real interest and importance. This is the fourth of his most exhaustive papers. All are accompanied by excellent drawings, and are valuable contributions to the anatomy of disease-producing insects.

Diseases and Deformities of the Foot. By JOHN JOSEPH NUTT, M. D. Illustrated. \$2.75. (New York: C. B. Treat & Co., 1913.)

The author says in his preface that this book is intended for those who have not made a special study of orthopedics. But is the average practitioner capable of treating the simpler deformities of the feet with such a brief work as this to guide him? We do not think so, and feel that these deformities should, whenever possible, be referred to the specialist. The best orthopedists frequently fail to secure good results in these operations, and a bungling operation only makes the condition harder to treat and cure. The very lack of details in a short treatise of this nature makes it unsuited to the needs of one ignorant of the subject, who if he wants to treat a club foot, should get all the information he can as to how to operate before attempting to correct the deformity, and not rely on a well-drawn outline sketch, such as this is.

Burdett's Hospitals and Charities for 1914. Being the Year Book of Philanthropy and the Hospital Annual. By SIR HENRY BURDETT, K. C. B., K. C. V. O. Twenty-fifth year. (London: The Scientific Press Limited, 28 and 29 Southampton St., Strand, W. C.)

The present issue of Hospitals and Charities is styled in an interesting preface, the Silver Jubilee Volume, because of the completion of the twenty-fifth year of continuous publication. To those who saw the early volumes the development of the work during the past few years is a matter of surprise and gratification.

We are told that the volume for 1914 contains accurate figures from the audited accounts of six thousand distinct institutions for the year ending December 31, 1912. No person who has not wrestled with the intricate statistics of a single hospital can adequately appreciate the immense labor involved in this annual review of the statistics of charity and philanthropy.

In addition to these statistical reviews of the operations of hospitals we find interesting accounts of several distinctive British organizations to foster and extend their work, such as "The King's Fund and the League of Mercy," "Hospital Sunday" and "Hospital Saturday." The apparent decline of the Hospital Sunday movement which seems to require each year a larger subvention from legacies and interest from invested funds seems difficult of explanation. In the United States the observance of Hospital Sunday was a direct importation from England, and as it did not grow out of any popular feeling, it is not strange that it has never had any adequate support, and outside of two or three large cities we now hear little about it. In England, however, it was wholly different. It is possible that "The King's Fund and League of Mercy" tended to draw away its supporters among the upper classes; and "Hospital Saturday" its friends in the laboring classes.

The comparative tables of the cost of nursing in the London and Provincial Hospitals respectively are full of interest. The cost of nurses, *per head*, to use the editor's phrase, in London in 1912 varied from fifty-four pounds at St. Bartholomew's to thirty-nine pounds eight shillings at Guy's; and outside of London from forty-three pounds six shillings at the Glasgow Royal Infirmary to thirty-two pounds eight shillings at the Dundee Royal Infirmary. A strong plea is made for more definite systems of accounting in every Nurses' Training School in order to determine the exact cost of maintenance. It is suggested that separate accounts be kept of every item of support, even where the Nurses' Home does not possess a separate kitchen. A separate kitchen requisition sheet is further suggested for each and every department of a hospital so that it may be shown what sums are expended for food, etc., per person upon the medical staff, the nursing staff, the employes and the patients. The practice of lumping together such expenditures to secure an average daily cost of support of all persons residing in the hospital irrespective of the varying circumstances and cost of maintenance is justly deprecated.

In view of the comparatively small number of convalescent hospitals or homes in America it is of interest to note that three hundred such institutions are to be found in the United Kingdom alone. It is evident that we need a much larger number.

The financial details of the expenditures of hospitals in Great Britain and America are thoroughly analyzed and deserve careful study by all hospital officers. It is to be regretted that comparatively few hospitals of the United States are thus reported because of the lack of uniform systems of recording expenditures. The leading hospitals of English-speaking countries owe it to themselves to agree at an early day upon a form of comparable statistics.

Bovine Tuberculosis and Its Control. By VERANUS ALVA MOORE, M. D., etc. \$2. (Ithaca, N. Y.: Carpenter & Co., 1913.)

Now that the subject of tuberculosis has gained a widespread attention, this book should find a large and interested public; for tuberculosis in cattle has assumed an integral and important part in the broad plan for suppressing the disease. It touches human pathology and hygiene, invades sociology and encloses pressing economic questions. In simple form Dr. Moore gives the essentials about bovine tuberculosis. The information is not exhaustive, but it is in general accurate and it is an advantage that the book is perfectly intelligible to intelligent laymen.

Disputed questions are treated with moderation and conservatively, especially for instance, the chapter on the value of tuber-

culin in diagnosis. The methods of eliminating tuberculosis from herds are given full consideration. Those interested in the establishment and maintenance of sanitary dairies should find the book invaluable.

Modern Problems in Psychiatry. By ERNESTO LUGARO. Translated by DAVID ORR, M. D., and R. G. ROWS, M. D. With a foreword by SIR T. S. CLOUSTON, M. D., LL.D. \$2.50. (Manchester University Press, 1913.)

The first edition of this work was published in 1909. No radical alteration has been made in this edition. The book is one which enjoys a well-deserved popularity owing to the clearness with which some of the more general problems in psychiatry are discussed, but on the other hand some of the more modern problems are practically not touched upon. According to Clouston however, who writes a foreword to the book, Lugaro has pointed out future lines of research more clearly and fully than almost any of the modern authors.

In the general introduction the relation of psychiatry to general medicine is discussed, and the importance of welding it with general clinical medicine is strongly emphasized. Chapters are devoted to the psychological problems, the anatomical problems, pathogenesis, etiological problems, nosological problems, and practical problems.

Throughout his work Lugaro discounts the importance of psychic causes in the etiology of mental disorders, and his somewhat formal point of view may be seen from the fact that of all factors he regards them as being the most insignificant.

Ophthalmic Diagnosis. By DR. C. ADAM, Berlin. Translated by M. L. FOSTER, M. D. Illustrated. (New York: Rebman Company, 1913.)

This is probably one of the best, if not the best, atlas of the internal diseases of the eye which has ever appeared. Not only are the pictures well nigh perfect, exhibiting the minutest changes in practically every disease, and altered condition of the fundus oculi met with, but the descriptions accompanying the same not only describe the plates, but furnish a wealth of accurate clinical and pathological information. The cases shown have been so carefully worked up and described that we regret that the author has not inserted the possible vision which each case had in every instance, while suffering with the pictured eye lesion. This would have made this work incomparable as a work of reference in medical-legal and court questions, as far as the internal lesions of the eye are concerned. This book deserves to be held in the highest esteem by all medical men.

Surgery of the Eye: A Hand-book for Students and Practitioners. By ERVIN TÖRÖK, M. D., and GERALD H. GROUT, M. D. Illustrated. \$4.50. (Philadelphia and New York: Lea & Febiger Publishers, 1913.)

There is nothing particularly new or novel in this work, nor are the operations described more accurately or better than in many text-books on the eye, which do not aim to be devoted exclusively to eye surgery. The work, externally, is of good size, but this is found to be due to large print, and large pictures, many of which are entirely unnecessary, rather than to an abundance of valuable subject-matter. Surely no one capable of doing eye surgery need be shown, by means of a full-page photograph, how to illuminate the eye-field with a hand lens, nor need he be shown how to apply ointment to the conjunctival cul-de-sac. What's the need of showing an eye surgeon how to apply lid retractors, giving two full pages to illustrate this simple procedure? Even in the text a large amount of the subject-matter is devoted to the unnecessary description of commonplace steps. To recapitulate, the beginner will not need this work, and the eye surgeon will likely have at his finger's

and all the details mentioned so laboriously, long before he is likely to want a book of this title. We consider the real worth of this book small, and have been disappointed in its perusal.

Ophthalmic Semiology and Diagnosis. By CHARLES H. BEARD, M. D. Illustrated. \$4. (Philadelphia: P. Blackiston's Son & Co., 1913.)

This is one of the most unsatisfactory books which has come to our attention recently. We recognize the fact that it is one of a number, which is embraced in the so-called "International System of Ophthalmic Practice," but we think that fact should not permit the desultory putting together of matter, as found in this volume. The author writes on subjects at his own whim, and lets others alone, of equal, or more importance. He does not limit himself either to the external diseases of the eye, or those visible with the ophthalmoscope, but has fragments, large and small, dealing with both; and then, too, most important omissions. There is a considerable amount of good matter on the retina, and its diseases, and so far as it goes the rest of the book is also good, but is not satisfactory in its present manner of presentation. Probably if the author had had his field more clearly defined for him he would have produced a work worth while, but in its present arrangement this book has but a limited sphere of usefulness.

Diseases and Injuries of the Eye. By WILLIAM GEORGE SYM, M. D., Edinburgh. Illustrated. \$2.50. (New York: The Macmillan Company, 1913.)

This is a very satisfactory small work on the eye, and unlike a large number of others, is not an abbreviated edition of some of the larger text-books, but is distinctly the author's own work, and in it, at times, he expresses his own opinion, sometimes at variance with the accepted one, in rather a positive tone. Not that the author aims to be argumentative, but he is simply positive in his own opinion. This is just as well for the student, who is thereby receiving almost personal instruction from a well-informed teacher. The author skilfully introduces the required amount of pathology and bacteriology along with his subject-matter. As a text-book to round out the ordinary daily work of the student in the eye clinic this book will be found to be helpful and valuable, even though the said student may have to refer to some larger work for more thorough study of some of the rarer conditions met with there. As an exposition of clinical ophthalmology as viewed by a Scottish writer this work will afford additional interest to American readers. It is an excellent little work, well printed, well arranged, well illustrated, and its system of therapeutics is definite, safe and conservative, and may be safely followed.

The Difficulties and Emergencies of Obstetric Practice. By COMYNS BERKELEY, M. D., and VICTOR BONNEY, M. D. Illustrated. \$7.50. (Philadelphia: P. Blackiston's Son & Co., 1913.)

This book differs from the usual text-book on obstetrics in that the authors have purposely omitted the physiology and management of normal pregnancy, labor and the puerperium, and confine their attention to the various abnormalities met with in the practice of obstetrics.

This book contains many excellent practical points for the student and practitioner, and more attention is given to the unusual disorders met with in obstetric practice than is possible in the usual text-book on obstetrics.

This book, however, is to be regarded rather as a practical guide, than a scientific work. Very scant reference is made to the literature, and there are no descriptions of the pathological and autopsy findings associated with abnormal conditions. Nor do the authors consider at any length the various unsolved problems met with in obstetrics.

The author's views on the toxæmias of pregnancy do not conform with the more modern teachings and they apparently regard all cases of eclampsia as being of nephritic origin.

Considerable space is devoted to the descriptions of the various obstetrical operations which are very good. As in most English works on obstetrics, the application of forceps to the sides of the pelvis, rather than to the sides of the child's head, is advocated.

The book is profusely illustrated with excellent original drawings.

Text-Book of Midwifery. By R. H. JOHNSTONE, M. D., etc. Illustrated. \$3.50. (New York: The Macmillan Company, 1913.)

In this small hand-book the author has covered the subject of practical obstetrics in a thorough but concise manner, and the book ought to prove of value to the student of obstetrics as well as to the practitioner.

The arrangement of the subject-matter does not differ radically from that of the usual text-book on obstetrics, the author taking up in order the anatomy of the pelvis and female genitalia, conditions met with in normal pregnancy, labor and the puerperium, and then considering the various pathological conditions met with during the same periods. Lastly, there is a section devoted to the various obstetrical operations.

The chapters on the implantation and early development of the ovum, with the formation of the placenta, are from the student's standpoint particularly good, and the author presents this difficult subject in a short but comprehensive manner. The chapters on the mechanism of labor, and the management of normal labor are excellent, no details being omitted.

The author's description of the various obstetrical operations are rather brief and the indications for the various operations are not discussed as extensively as might seem wise. In common with most English authors, the writer, in his description of the various forceps operations, advocates the "pelvic" application of the forceps, instead of the method usually taught in American schools, namely, the application of the forceps blades to the sides of the child's head.

The illustrations in the book have been largely drawn from other text-books on obstetrics, due credit for which has been given to the various authors from whose works they are taken.

Text-Book of General Pathology. Edited by M. S. PEMBREY and J. RITCHIE. \$5. (New York: Longmans, Green & Co., 1913.)

In this text-book, edited by Pembrey and Ritchie, an effort has been made to present general pathology from a physiological or functional standpoint. This effort is indicative of the recent trend of thought; the authors, however, among whom are many of the most prominent British pathologists and physiologists, must suffer the disadvantage of doing something novel and unaccustomed. The great difficulty is to preserve unity and proportion in such a vast subject.

In the preface the object of the work is stated, and it is added that, where the combined efforts of pathology and physiology have been unproductive, conventional lines are followed. As a consequence, the book is divided rather sharply into two parts, the one in the accustomed manner, the other showing the results of modern laboratory methods. The conventional chapters are gathered toward the beginning, the others at the end. In the first category the writers have done their work adequately. Inflammation is considered in a very full and clear manner, and the nervous system has a long chapter by Dr. Mott.

In the latter half of the book the material is more characteristic. Much data of an experimental nature bearing upon normal and abnormal body processes is included, and fruitless anatomical observations are avoided. The subjects are arranged in an unusual manner, the anatomical order being again ignored, and

functional entities grouped together. The chapter on respiration is especially pleasing and satisfactory, and may well serve as a model. Those upon degenerations, temperature, hepatic disease, carbohydrate metabolism, and gout, contain stores of useful and suggestive information for the student, presented fully in a clear and good style.

On the other hand, a few chapters, as those concerning digestion and circulation, fall below the general standard, while the kidney is much slighted. A little tendency is observed here and there to state opinions in such a way that they may possibly be mistaken for accepted facts.

Throughout this book a working knowledge by the reader of chemistry, physiology, and laboratory procedure is assumed. In this and in its general aim it is to be commended as a step in the proper direction.

A Clinical Manual of Mental Diseases. By FRANCIS X. DERCUM, M. D., PH. D. \$3. (Philadelphia and London: W. B. Saunders Company, 1913.)

This book is based upon the annual course of lectures delivered by the author at the Jefferson Medical College. The classification adopted is exceedingly cumbersome, and unfortunately leads to a great deal of very unnecessary recapitulation.

The symptomatology of the various clinical entities is faithfully described, but it is all presented in such a formal way, without any case histories, and with practically no attention paid to more recent teachings in psychiatry that it is exceedingly unsatisfying. Particularly is this the case when one comes across such statements as: "Manic-depressive insanity is probably due to a toxin; the recoveries from the individual attacks suggest the formation of an antitoxin."

Then again it is rather surprising in this age to find hysteria considered in a chapter where mental diseases related to somatic affections are discussed.

In considering the eye-signs of general paralysis it is stated that in addition to the light reflex being lost that the reaction of accommodation is sooner or later involved, and then not content with this it is further emphasized that "the more advanced the case the more likely is there to be loss of accommodation, and in almost all cases the loss is present in both eyes simultaneously."

To allow him to make such statements the author's experience must surely be unique.

There are so many questionable statements made throughout the book that one could not conscientiously recommend it as a safe guide either for the physician or student.

Clinical Pathology. By P. N. PANTON, M. A., M. B. 446 pages. \$4. (Philadelphia: P. Blakiston Son & Co., 1913.)

The author's attempt to produce a book intermediate in size between the larger and smaller works on "Clinical Pathology," which would meet the demands of the student and practitioner, has been unsuccessful, and for obvious reasons. Medical literature of the day has no legitimate place for this type of compend which sacrifices scientific accuracy and scope of statement to the ambition of including within one volume the subjects of blood-bacteriology, puncture fluids, urine, the alimentary system, the eye, skin, respiratory tract and histology. Of necessity, brevity of statement and the lack of detailed discussion, combined with the absence of any references to the literature, tend to foster the all too prevalent habit of drawing sweeping conclusions from insufficient data and for this reason especially the book is unsuited to the student. For the practitioner there exists a vast amount of

indefinite disjointed statements, tests with scanty interpretations and a general arrangement of subject-matter calculated to discourage further reference to the book. Errors of omission are not uncommon—such as the absence of the polariscopic determination of sugar, newer methods of blood counting, or the estimation of the degree of pleocytosis in the cerebrospinal fluid. One and a half pages suffice to describe all forms of malaria. Such statements as are made with respect to the differentiation of amœbæ, the constancy of the amount of complement in guinea pig's serum, and the taking of 10 cc. of spinal fluid with impunity are a few of many questionable statements; while the six lines devoted to the Calmette reaction leave one with the feeling that the author is not aware of the real truth of the matter.

Illustrations, though few in number, are, for the most part good, and the text is quite free from typographical errors.

The Elements of Bacteriological Technique. By J. W. H. EYRE, M. D., etc. \$3. (Philadelphia and London: W. B. Saunders Company, 1913.)

The second edition of Eyre's Bacteriological Technique rewritten and enlarged has just been published by Saunders. It consists of over five hundred pages, devoted entirely to the technique of bacteriology, divided into twenty-one sections.

These sections deal with such subjects as: Common glass apparatus, methods of sterilization, the microscope, staining methods, methods of identification and study, experimental animal inoculations and bacteriological analyses.

The material is presented in logical sequence, each subject being well described, and special attention being paid to all essential details. The illustrations are numerous and of considerable merit, each one having its own intrinsic value in being accurate and suggestive.

Several chapters deserve special note, as for instance, the opening chapter which gives a complete list of the glass apparatus commonly used in bacteriological work, and is followed by a useful consideration of the various methods of sterilization. The section entitled "The Microscope" affords a brief but comprehensive description of this instrument, and includes a discussion of the various accessories necessary for microscopical work. The section on "staining methods" is especially useful in giving a detailed description of the composition of the various dyes and all the latest methods of differential staining. A brief description with the classification of fungi preceding a short discussion on the life cycle of bacteria affords a splendid comparison between the two classes of microscopic life. Thus the relationship from the evolutionary standpoint is made clear. The chapter on "Methods of Identification and Study" is especially worthy of note. By a detailed study of the macroscopical, microscopical, biochemical and physical properties of various organisms a thorough and complete method for identifying them is given. The discussion on technique in relation to experimental animal work in bacteriology, though somewhat detailed, is worthy of considerable attention.

The treatise is concluded by a consideration of the technique of both quantitative and qualitative bacteriological analyses of water, milk, sewage and foodstuffs, which are highly important from the standpoint of practical or applied bacteriology. The methods outlined are the ordinary methods universally employed without any additional new ones.

This text-book is primarily intended as a laboratory guide for beginners. It may be highly recommended for the purpose for which it was primarily intended, as it is exceedingly thorough and gives all of our important modern methods.

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CONTINUOUS PROPAGATION OF AMŒBIC DYSENTERY IN ANIMALS.

By WALTER ALBERT BAETJER

AND

ANDREW WATSON SELLARDS.

(From the Medical Clinic of The Johns Hopkins Hospital.)

OUTLINE.

- I. Introduction and literature:
 1. Propagation of entamœbæ in animals is limited, as a rule, to three or four passages.
 2. General conclusions that the strain of entamœbæ dies out because of degeneration of the entamœbæ with consequent loss of virulence.
- II. Method of transmission:
 1. Method of inoculation.
 2. Selection of infective material.
 3. Choice of animals with especial regard to age.
 4. Selection of suitable temperature and diluting agents in the handling of the infective material.
- III. Behavior of a strain of dysentery on successive passage in animals:
 1. Effect on the clinical course.
 2. Effect on the entamœbæ.
 3. Effect of the accompanying bacteria.
- IV. Relation of the entamœbæ to the general laws of the protozoan and bacterial infections.
- V. Correlation of these data with previous results:
 1. Loss of strain by bacteriæmia in animals.
 2. Failure of infection on account of method of inoculation.
 3. Failure of infection on account of choice of material.
- VI. Conclusions that passage in animals is not self-limited.

The infection of lower animals with amœbic dysentery presents some exceptional and complicated features, both in the

variation in individual susceptibility and in the subinoculation from one infected individual to another, for the transmission of the disease through a series of animals. Amœbic infection with the reproduction of its characteristic symptoms has frequently been produced in several species of lower animals. Even under optimum conditions, however, the percentage of successful infections is extremely variable, ranging, with a few exceptions, from twenty-five to fifty per cent. The most unexpected feature develops upon subinoculation from animal to animal, when it is found that the infection invariably dies out. Werner¹ succeeded once in carrying a strain of entamœbæ, identified as hystolytica, through six passages. This limitation of the number of passages was explained on the basis of biological changes in the entamœbæ. Werner concludes that a strain becomes avirulent after a few passages to the extent that it not only does not produce symptoms, but apparently that it fails even to parasitize its host without producing symptoms.

Hartmann² found that the infection invariably died out in the second or third passage on account of degenerative changes which occurred in the entamœbæ. He concludes that kittens are naturally very refractory to infection. Wenyon³ was also unable to carry a strain of dysentery further than four passages, but his conclusions differ radically from the preceding

observers. There was no evidence of any diminution in virulence and the strain was lost through accident. Wenyon concludes that it should be possible to propagate a strain of entamœbæ indefinitely in animals. Darling⁴ has confirmed and extended Hartmann's observations. He concludes that the pathogenic entamœbæ not only become avirulent on passage, but that they undergo definite changes in their morphology and life cycle; the trophozoites diminish in size corresponding to *Entamoeba minuta* and the tendency to encystment increases.

These authors, with the exception of Wenyon, distinguish carefully between two pathogenic strains: Namely, *Entamoeba histolytica* (Schaudinn) and *Entamoeba tetragena* (Viereck). Werner investigated several strains of entamœbæ and distinguished between histolytica and tetragena on the basis of morphological differences. As regards their biology, Werner could discover no constant differences either as regards their virulence, the number of passages that could be obtained in animals, the course of the disease in animals, and the pathological effects that could be produced. Hartmann's statements apply to *E. tetragena*. Darling, on the basis of Werner's results and his own experience, has emphasized more the difference in infecting power between the two types. According to him the histolytica-like strain can be carried as high as six passages, while the tetragena type rarely infects beyond two generations and often dies out in the first series of animals inoculated. The loss in virulence and infecting power in both types are, according to Darling, associated with definite morphological changes in the organisms, notably in the transformation which he has described as the "small generation," a form assumed by the organism in the generation before encystment occurs. Apparently there has been no attempt to propagate the parasitic but non-pathogenic *Entamoeba coli*, and it is evident that the pathogenic entamœbæ have not been propagated except for a limited number of passages in lower animals. If one accepts that there are two species which are pathogenic for man, this statement applies equally well to either species. In 1911, however, Walker⁵ reported observations which led him to conclude that two distinct species have not yet been established and that *E. histolytica* and *E. tetragena* are identical. He concludes that the morphological differences in the vegetative state in *E. histolytica* and *E. tetragena* which were originally described by Viereck¹⁰ and Hartmann are extremely inconstant and that both of these types form their propagative stage in the same manner, *i. e.*, by the production of a four nucleated cyst. The reproduction by the process of budding, which, according to Schaudinn's description, occurs in histolytica, was not observed by Walker. The identity of these two species has since been accepted by Craig,⁶ Wenyon,³ and in its essentials by Hartmann⁷ and by other observers. It seems to us that the evidence for the establishment of *E. tetragena* as a distinct species is wholly insufficient. Accordingly, we shall tentatively use the term *E. histolytica* of Schaudinn to include the four nucleated propagative stages discovered by Viereck until the nomenclature is definitely established. Hartmann⁷ has recently suggested that the ter-

minology should properly revert to that suggested by Councilman and Lafleur.⁸ In case strains of *E. histolytica* with characteristically distinct propagative stages should be established, it might be desirable to retain the term "tetragena" to indicate a variety of *E. histolytica* but not as a distinct species of entamœbæ.

The determination of whether the propagation of amoebic infection in lower animals is self-limited becomes of interest from several standpoints. It is naturally of importance in the determination of the laws of protozoan infection and immunity. Moreover, in the absence of any methods for cultivating either the pathogenic or parasitic entamœbæ, the infection of animals is extremely desirable in order to obtain a suitable supply of material for study. This applies not only to the localities where acute cases are rare, but also to the endemic areas in the tropics. The infection of animals is so uncertain that only a minimum of experimental work has been done upon morphology, pathogenesis, and experimental therapy.

Methods of Transmission.—In attempting the propagation of a strain of dysentery in animals, the literature indicates that the routine of various workers has been fairly uniform. Accordingly, we have followed the usual technique as closely as feasible. Cats or kittens were selected. In the choice of the various routes of infection, we did not have occasion in this series to make use of feeding experiments. The majority of animals were inoculated by rectal injection. However, in order to secure the first transfers from man to lower animals, the infective material was injected directly into the cæcum. A small incision was made in the abdominal wall, the syringe needle was inserted through the wall of the cæcum, and the injection was made directly into the lumen. This procedure gave distinctly better results than were obtained, even under the most favorable conditions, by other methods of injection. The explanation for the high percentage of infections which was obtained probably depends upon a number of minor factors. Other strains of entamœbæ are under investigation at present and the discussion of this procedure will be reserved for a subsequent communication.

The first strain of dysentery with which we worked occurred as an initial attack in a negro, who had contracted dysentery in North Carolina with a history of three months duration. Duplicate injections of about 3 cc. each of a bloody mucous stool rich in trophozoites were made into the cæcum by laparotomy, in an adult cat and a half-grown kitten. After an incubation period of seven days, both animals became acutely infected. The adult cat developed a mucous diarrhoea with very large amœbæ and death resulted after sixteen days. The kitten showed a bloody dysentery with smaller organisms, and lived for nineteen days. Subinoculations were made from both animals immediately after death by injections into the cæcum in four animals. In all four death occurred promptly in one to five days from peritonitis, accompanied usually by septicæmia.

A little later a second case of dysentery was admitted to the hospital. This was an acute relapse, the original infection having been contracted in the Philippines a year and a half

previously. During the first fourteen months of the disease there had been several acute relapses with complete absence of symptoms in the interim. He was then treated with emetine and temporarily relieved. After four months he returned to the hospital in another acute attack. Emetine treatment was begun at once, and the patient had been receiving $\frac{2}{3}$ grain, hypodermically, daily for three days before the stools were obtained from which the first animals were inoculated. In commencing the propagation of this strain especial attention was given to the following features:

1. Subinoculation from animal to animal at the first appearance of clinical symptoms in preference to waiting for the death of the animal or till the later stages of the infection.
2. Selection of suitable temperature and diluting agents in the handling of the infective material.
3. The selection of kittens (half-grown or younger) rather than adult animals.
4. The injection of the infective material directly through the lumen of the bowel into the cæcum in addition to the injections by rectal tube.

The details of this routine were comparatively simple. As far as possible the transfers were made at the first appearance of bloody mucous discharges in an infected individual. Only fresh material was used for injection. Usually not more than one hour elapsed from the time the specimens were obtained till the injection of all animals was completed. When the transfers were not made at the beginning of the infection the animals were usually sacrificed in preference to waiting for post mortem material. The contents of the lumen of the bowel when faecal or purulent were discarded and amœbæ were obtained by scraping the mucosa of the intestine. In practically all cases the injected material consisted almost exclusively either of blood and mucus with little or no macroscopic contamination with faeces and with relatively few bacteria on microscopic examination. Trophozoites were present usually in large numbers in all the material which was injected and were not infrequently accompanied by an abundance of cysts. For the intracæcal injections it was found that relatively large pieces of mucus and blood could be forced through a needle of moderate bore, provided that no firm particles were present. When necessary, the material was suspended without emulsifying in tap water or in 0.2 per cent salt solution in tap water. Stronger concentrations of salt were deleterious. As far as possible the pieces of mucus were left intact, for it was found on microscopical examination that the amœbæ in vitro were preserved better in the fluid in which they occurred in the body than in any artificial solutions. The concentrations which were tried were tap water and solutions of technically pure sodium chloride in tap water of 0.1, 0.2, 0.3, 0.4 and 0.5 per cent dilution. The amœbæ in the specimens of blood and mucus from the intestine were best preserved without the addition of any foreign fluids. Of the diluting fluids 0.2 per cent salt was a little better than tap water alone and 0.5 per cent salt was the poorest. The optimum concentration of salt would probably vary within narrow limits according to the nature of the material in which

the amœbæ were found. Furthermore, it was found that, in accordance with the preservation of other tissues, the amœbæ, though less active, retained their vitality better, at a room temperature of 20°C. than at incubator temperature.

Young animals proved to be distinctly more susceptible than adults. The youngest animals used weighed about 400 grams and these proved to be very suitable. The susceptibility varied directly with the age and we did not find that an optimum susceptibility occurred in kittens that were about half-grown as has been suggested. Injections directly into the cæcum were used more particularly for the injection of adult animals and in the early transfers. As the virulence increased, injection by high rectal tube proved to be more suitable than the intracæcal inoculations.

The following observations were kept as a routine:

1. Examination of the material which was injected by fresh and stained preparations.
 2. Determination of the incubation period.
 3. Observations upon the course of the infection in animals and when possible stained preparations of amœbæ obtained late in the course of the infection.
 4. Determination of the occurrence of bacterial septicæmia with especial reference to the cause of death in fatal infections.
- For the stained preparations the material was fixed by the wet method, and carried wet throughout the entire process of staining and mounting. The technique was essentially that used by Walker.⁵ Smears were made by teasing out the material on cover slips without exerting any pressure. When the specimens were too viscous to spread in this manner, they were first teased out in a little tap water or in 0.2 per cent salt solution in tap water. These smears were floated at once face down on Zenker's fluid for five to ten minutes and then washed with one or two changes of water for several hours or over night in distilled water. They were then stained intensely in Delafield's hæmatoxylin for ten to thirty minutes and washed for several hours in tap water. This routine did not necessitate controlling the washing by microscopic examination. The stains were then cleared in alcohol (25-50-75 per cent and absolute) then in oleum origani vulgi and mounted in balsam.

The incubation period which is recorded is the clinical incubation period; *i. e.*, the time of appearance of definite clinical symptoms consisting in the passage of mucus and blood containing active entamœbæ. This seemed distinctly preferable to the determination of the earliest time at which entamœbæ could be identified microscopically in the stools, especially since with the extremely short incubation period which subsequently developed, and with the large injections in small animals, the appearance of entamœbæ in formed stools would be no proof that multiplication or parasitization had occurred. Moreover, the determination of the time of appearance of clinical symptoms was extremely satisfactory. The normal condition of the animals was very constant. In over 60 individuals which were kept under observation, the stools were regularly formed with the exception that in the very young kittens, six or eight weeks old, the stools were soft, but uniformly free from blood and mucus. After in-

oculation, the infection appeared as an acute outbreak characterized sometimes by a day in which one or more soft stools were passed, followed within a day by the discharge of both blood and mucus, and the presence of numerous active amœbæ. Whenever possible, this first discharge of blood and mucus was used for inoculation.

Blood cultures were made by aspiration from the heart according to the usual routine when the animals appeared ill, when they were sacrificed, or at the time of death. Septicæmia was encountered just before death in the majority of instances. In the early inoculations by laparotomy into the cæcum there was no difficulty whatever from peritonitis after the puncture of the cæcum even when a large syringe needle was used and the injected material was rich in faecal matter. Subsequently, peritonitis became extremely difficult to avoid although the injected matter consisted macroscopically of blood and mucus and a small needle was used followed by careful cautery of the puncture wound.

Effect on the Clinical Course.—The general results which we obtained with this strain were somewhat unexpected. The entamœbæ, instead of losing their pathogenicity after several passages, increased remarkably in virulence. The incubation period in the four animals used for the first three passages was almost exactly six days with a duration of the disease lasting as long as six and a half weeks. These periods were shortened until in the sixth passage an incubation period of two and three-quarter days was obtained, with death occurring one day later. Not only did the virulence increase, but the trophozoites, instead of diminishing in size to the minute race which has been described, remained active and vigorous without any suggestion of degenerative changes. The strain became so active that it was not a simple matter to insure its continuation. A comparatively large number of animals were required to avoid absolutely the possibility of the loss of the strain through accident. On some occasions as many as six or seven animals were required to insure a single passage.

It soon became apparent that the changes in virulence and morphology which had been described as occurring constantly upon subinoculation of entamœbæ did not apply to this strain. When this was well established the number of animals used for any one passage was reduced to two or three. After eleven successive passages had been secured the strain was allowed to die out. All of the infected animals reacted typically—both clinically and pathologically; the morphology of the entamœbæ found in them was characteristic. The incubation period in the ninth, tenth and eleventh passages in a total of five animals ranged from five to nine days. This return to the longer incubation period was perhaps due in part to the continued passage of the strain by rectal injections rather than by direct inoculation into the cæcum, but also to the use of material taken several hours post mortem. The accompanying diagram (No. 1) shows some of the essential features of the successful inoculations.

Effect on the Entamœbæ.—Morphologically, the typical organisms show no degenerative changes either in fresh or

stained preparations provided these are made from suitable characteristic specimens. This strain after passage through kittens showed no deterioration in the organisms in regard to size, motility, staining reactions, and structure of the nucleus. Encystment frequently occurred with the four nucleated cyst predominating, but the vegetative forms were always present in excess of the cysts. On the other hand, however, there were numerous opportunities for obtaining degenerated types corresponding to those described by Hartmann^{1 c} and by Darling.^{1 c} The organisms often became much less typical in chronic cases of long standing and in acute cases when bacterial complications developed such as a bacteraemia or a purulent bacterial enteritis. Moreover, degenerative forms were frequently found in stools which, though freshly obtained, had often remained for some hours in the lumen of the intestine where the entamœbæ were extensively contaminated with faeces and were subject to bacterial fermentation and various deleterious influences. When such animals were sacrificed, typical entamœbæ were found higher up in the intestine or in the scrapings from the mucosa. In this connection it may be

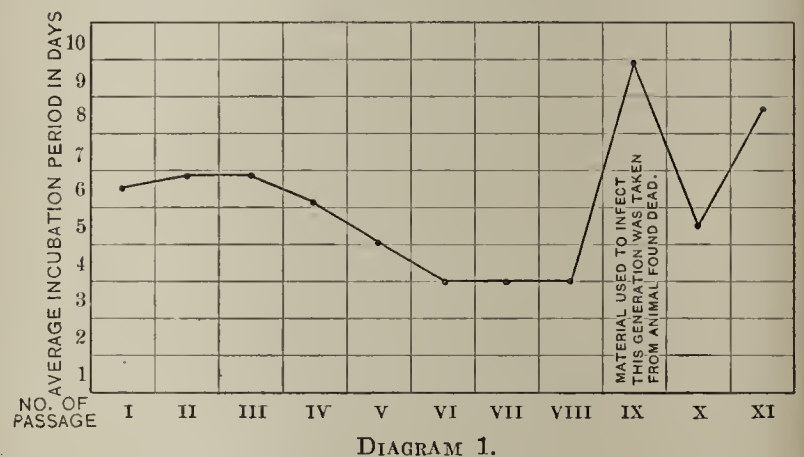
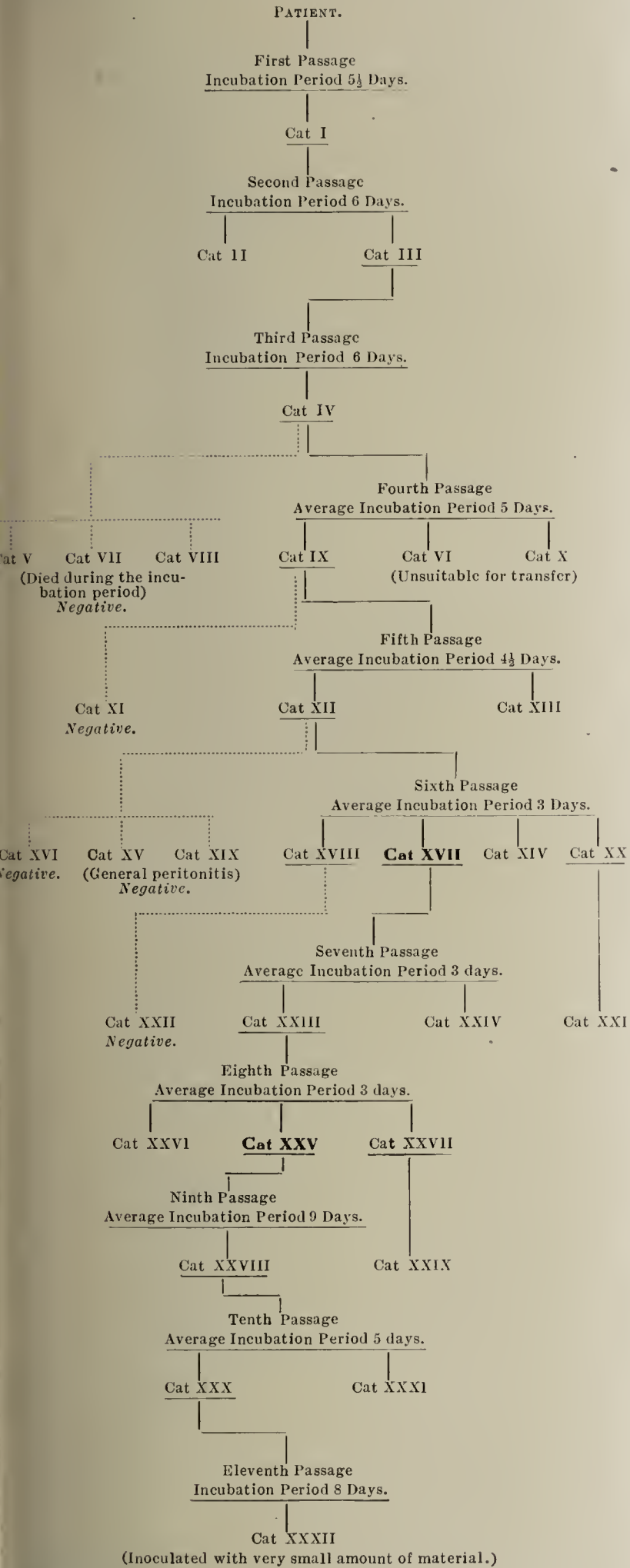


DIAGRAM 1.
This diagram includes the average incubation period of all animals used in each generation except two adult cats. These were not included because adults are known to be unfavorable subjects with longer incubation periods and do not offer fair comparison with the incubation period of younger and more susceptible animals which were used in the other inoculations.

noted that some of the degenerations described by Darling occurred in specimens which were obtained post mortem. The accompanying plate illustrates typical specimens of organisms obtained from the patient, and from the eleventh passage in cats. Small degenerative forms occurring in the second passage are also included. Biologically, there was a definite increase in the virulence of this strain which was shown principally by the progressive shortening of the incubation period in the successive passages.

There were two conditions which were especially difficult to control; namely, (1) bacterial infection, and (2) in a few animals, the failure of the amœbæ to infect even under optimum conditions. The accompanying diagram (No. II) shows the total number of animals used in the individual passages with the general result in each case. Table I gives the details of the animals which became infected and Table II those which did not become infected. More complete protocols are given at the end of the paper.

DIAGRAM II, SHOWING THE NUMBER OF ANIMALS USED AND THE GENERAL RESULTS.



The eight animals which failed to contract dysentery are grouped on the left and are connected by the broken line.

TABLE I.
DETAILS OF ANIMALS WHICH BECAME INFECTED.

No. of passage.	Size of cat.	Method of inoculation.	Incubation period.	Remarks.
1st passage.	$\frac{1}{4}$ grown.	Intracæcal injection.	5-6 days.	Killed after 9 days.
2d "	$\frac{1}{2}$ "	" "	6 "	Died after 44 days.
2d "	$\frac{1}{2}$ "	" "	6 "	Died after 31 days. Blood culture +.
3d "	$\frac{1}{2}$ "	" "	6 "	Died after 10 days. Blood culture +.
4th "	$\frac{1}{2}$ "	" "	4 "	Died after 5 days. Blood culture +.
4th "	Rectal tube injection.	6 "	Killed after 7 days. Blood culture +.
4th "	$\frac{3}{4}$ "	" "	7 "	Killed after 90 days.
5th "	$\frac{1}{4}$ "	Intracæcal injection.	5 "	Died after 9 days. Blood culture +.
5th "	$\frac{1}{2}$ "	Rectal tube injection.	4 "	Died after 5 days.
6th "	$\frac{1}{2}$ "	Intracæcal injection.	5 "	Died after 66 days. Blood culture +.
6th "	$\frac{1}{2}$ "	Rectal tube injection.	3 "	Died after 27 days. Blood culture +.
6th "	$\frac{1}{4}$ "	" "	3 "	Died after 4 days. Blood culture +.
6th "	$\frac{1}{4}$ "	Intracæcal injection.	1 "	Died after 1 day.
7th "	$\frac{1}{8}$ "	Rectal tube injection.	3 "	Died after 3 days. Blood culture +.
7th "	$\frac{1}{8}$ "	" "	3 "	Killed after 4 days. Blood culture -.
7th "	Adult.	" "	15-20 "	Recovered.
8th "	$\frac{1}{8}$ grown.	" "	3 "	Died after 4 days.
8th "	$\frac{1}{8}$ "	" "	3 "	Died after 10 days.
8th "	$\frac{1}{4}$ "	" "	3 "	Died after 7 days. Blood culture +.
9th "	$\frac{1}{4}$ "	" "	9 "	Killed after 9 days. Blood culture +.
9th "	$\frac{3}{4}$ "	" "	16 "	Died after 27 days.
10th "	$\frac{1}{4}$ "	" "	8 "	Died after 8 days.
10th "	$\frac{1}{4}$ "	" "	20 "	Died after 22 days.
11th "	$\frac{1}{8}$ "	" "	8 "	Killed after 11 days.

TABLE II.
DETAILS OF ANIMALS WHICH DID NOT BECOME INFECTED.

No.	Size of cat.	Method of inoculation.	Time and cause of death.
Cat V.	$\frac{1}{2}$ grown.	Intracæcal injection.	4 days after injection. Sudden death; autopsy negative; blood culture +.
Cat VII.	Adult.	" "	7 days after injection. General peritonitis.
Cat VIII.	"	" "	7 days after injection. General peritonitis.
Cat XI.	"	" "	3 days after injection. General peritonitis.
Cat XV.	$\frac{1}{2}$ grown.	" "	4 days after injection. General peritonitis.
Cat XVI.	Young adult	Rectal tube injection.	No signs of infection. Died two months later from other causes.
Cat XIX.	$\frac{3}{4}$ grown.	Intracæcal injection.	1 day after injection. General peritonitis.
Cat XXII.	$\frac{1}{8}$ "	Rectal tube injection.	25 days after injection; cause of death unknown. Autopsy negative.

Effect on the Bacteria.—The bacteria interfered seriously with the laparotomies. In many instances it was evident from the anatomical lesions that the bacteria did not gain access to the peritoneum through the puncture wound of the syringe needle in the cæum, but that they were able to penetrate the intestinal wall directly. Frequently the serous coat of the intestine was intensely inflamed for a distance of several inches. This inflammation occurred sometimes in the large intestine, but often in the small intestine and bore no definite relation to the puncture wound. There was always an accompanying general peritonitis and also a septicæmia. Moreover, these complications did not occur only in those animals in which a laparotomy was performed; the injection per rectum

of some of the animals resulted in a general septicæmia. Frequently this septicæmia was fatal before the incubation period of the entamœbæ had expired. This behavior was rare, however. In the majority of animals no septicæmia occurred until after the development of lesions in the intestine. In no case, however, did an animal die of an uncomplicated amœbic infection, but in all fatal cases there was a secondary septicæmia. This invasion was not only secondary, as a rule, to the amœbic infection, but it often came on very late; the blood culture was sterile in one instance only when taken in an advanced stage of the dysentery. The bacteræmia, therefore, though a secondary factor, is important in its bearing upon the cause of death in this series of animals.

It was also noted repeatedly that the development of septicæmia, or of extensive peritonitis, resulted in a failure of the entamœbæ to cause infection. This is mentioned on account of its direct bearing upon the possible explanation of the loss of the strain reported by Wenyon. In one of his animals the protocol records the development, not only of septicæmia, but of pyæmia. We have, therefore, in this strain reported by Wenyon and in the two strains reported in this paper, examples of the frequency and importance of the secondary invasion by bacteria. The records of the strains propagated by Werner and Darling do not give any information in regard to the influence of the accompanying bacteria.

On account of the importance of this secondary invasion, the various bacteria obtained at blood culture were studied to determine whether one or several species were carried over into the blood in any given individual and whether a single strain was carried through all the animals or whether several species were involved. An examination of all the cultures, except two, from the second to the ninth passage, inclusive, showed a pure culture of a single organism. This was a small streptococcus forming short chains and producing identical culture reactions on ordinary media. In one animal of both the third and fourth passages, the cultures contained a bacillus in addition to the usual streptococcus.

As regards the second source of difficulty it has been an almost universal experience that not infrequently infection fails to take place even under the most favorable conditions. Thus, when a series of young kittens are inoculated with fresh blood and mucus rich in trophozoites and cysts, a certain number of them will frequently escape infection. The explanation of this has not been investigated rigidly, but it is apparently due to a variety of self-evident accidental circumstances rather than to a natural insusceptibility of these individuals.

Relation to the General Laws Governing Infectious Processes.—This strain of entamœbæ, instead of constituting an exception, conforms to the general laws governing infectious processes. It serves to illustrate very well certain features of infectious diseases which are especially characteristic of the protozoa. The onset of the disease was acute. The course terminated fatally in the first attack or became chronic. It did not run an acute self-limited course, ending in death or complete recovery, such as occurs in some bacterial diseases and

certain conditions of unknown etiology; *e. g.*, Asiatic cholera and yellow fever. There was no evidence from the clinical symptoms that one attack of dysentery conferred any immunity. When the condition of a carrier was developed, the infected individual did not enjoy freedom from symptoms, but was subject to acute relapses. As with many bacterial and protozoan parasites, the rapid passage of this strain through a series of individuals produced an increase in its virulence. The original incubation period of six days, which was required for the production of bloody mucous stools containing motile amœbæ, was shortened to two and three-fourths days by five passages. The total course of the disease from the time of inoculation was shortened in this instance to four days. This shortening was due, in part, to the early development of bacteræmia and an increase in the virulence of the accompanying bacteria. There was nothing which suggested in any way that the early appearance of amœbæ in the bloody mucous discharges could be connected with changes in the bacterial flora of the intestine. It is to be assumed that the exact details of behavior would vary with the individual strain. Thus, if a less virulent strain from a chronic case were injected into adult animals, there would surely be a smaller percentage of infections with less severe symptoms, and some strains might be comparatively difficult to propagate. Nevertheless, we feel that, under favorable conditions, the general rule will be that the passage of a strain will not be self-limited. Indeed, it would be of considerable interest, epidemiologically, if amœbic infection in susceptible animals died out after a few passages from one individual to another. If this were proved to be true, then amœbic dysentery, upon introduction in a susceptible species in an uninfected zone, would almost necessarily die out of itself, instead of becoming endemic.

Correlation with Previous Results.—The increase in virulence in this strain after a comparatively short number of passages does not exclude the possibility that a long continued passage through a great many animals might attenuate the virulence, as sometimes happens in the case of trypanosomes for example. The conclusion, however, is definitely refuted in this instance, that the entire strain necessarily undergoes morphological degenerations in that the virulence is lost, and that a strain dies out after at most from four to six passages. The question arises as to whether this strain constitutes an exceptional case or whether it represents the typical behavior of the pathogenic entamœbæ. An examination of the conditions governing the infection suggests that it is possible to correlate these apparently contradictory results. The conclusion that the passage of dysentery is self-limited is based upon two considerations; namely, that the parasites lose their virulence since the animals fail to become infected, and that the morphology of the amœbæ shows degenerative changes. In regard to the failure to infect, it must be remembered that several explanations as well as loss of virulence suggest themselves. In the first place the infection by feeding or by inoculation per rectum is extremely uncertain. The most unfavorable results are reported by Walker,* in Manila; with optimum infective material, no symptoms and no parasitization occurred

in thirteen animals representing three species. The uncertainty of feeding experiments and of injections per rectum as compared with the direct injection through the wall of the cæcum may account for some of the failures.

The effect of the bacteria which happen to accompany the entamœbæ is striking. In both of the strains reported in this paper and in that reported by Wenyon it has proven a troublesome factor. An examination of diagram No. II will show how easily this strain might have been lost purely through the effect of the accompanying bacteria. In two instances at crucial stages, its passage depended on the results in a single animal, although considerable precaution had been taken to secure a number of infected animals. It is not improbable that the selection of material at the onset of symptoms is advantageous both on account of the large numbers of active amœbæ that are obtained and also because the bacteria are somewhat less abundant.

In regard to the morphological changes which have been emphasized particularly by Darling, it is noteworthy that these also depend, in part, upon whether the entamœbæ are studied at the onset of symptoms or late in the course of the disease after the infection has become subacute or chronic. It is quite possible that long continued growth in one host with the possibility of specific reaction on the part of the host may produce changes in the infecting organisms, whereas the rapid passage from one susceptible animal to another might not afford any opportunity for the development of such changes. Thus, in some animals in our series the entamœbæ were perfectly typical at the onset of symptoms, but as the disease became chronic the entamœbæ became smaller in size, fewer in numbers, and less actively amœboid. Moreover, in the examination of the specimens it frequently happened that stools, though they were obtained perfectly fresh, contained small degenerating forms. It was evident that this was due to the retention of the stool in the lumen of the bowel under conditions which were not favorable to the growth or preservation of the amœbæ; on examining freshly obtained washings or on sacrificing such animals typical active organisms could usually be secured. Thus, there are many conditions arising in an animal which may result in the production of degenerative forms of entamœbæ. It must be emphasized that the occurrence of degenerative forms does not exclude the presence of perfectly typical forms at the site of the active lesions. Naturally, the sacrifice of an animal and an autopsy may be necessary to demonstrate the presence of typical organisms. When these degenerations do appear they may be the result of accidental complications in distinction to the explanation offered by Hartmann that the natural insusceptibility of cats sets up degenerative changes in the entamœbæ.

From these considerations we feel that there is not sufficient evidence to support the view that the passage of amœbic dysentery in animals is self-limited. The following factors must be taken into account in considering the explanation of the results that are reported in the literature:

1. Some of the strains may have been lost on account of the virulence of the accompanying bacteria.

2. The virulence of the entamœbæ may have been lost by re-inoculating late in the course of the infection of a given individual rather than at the first onset of symptoms.

3. Rectal injections of trophozoites have proven definitely less effective than direct inoculation through the wall of the cæcum into the lumen.

4. The degenerative changes in morphology which have been described can be explained in part by the nature of the material which was selected for examination.

In view of these considerations we feel definitely that the previous failures were due, like Wenyon's, to accident, and not to any inherent changes occurring in the entamœbæ as a result of the subinoculation.

SUMMARY.

1. Two strains of amœbic dysentery were investigated with the object of securing continuous propagation by subinoculation through a series of animals. The first strain was lost in the second passage by accident. The second strain was carried through eleven successive passages in kittens.

2. This strain increased in virulence and no degenerative changes appeared in the morphology of the entamœbæ obtained at the site of active lesions. The characteristics of the clinical course and pathological lesions were retained throughout the eleven passages.

3. The propagation proved to be considerably complicated by the virulence of the accompanying bacteria.

4. The successful propagation of one strain through eleven passages in animals, with an increase in virulence of the entamœbæ and a retention of the typical features of their morphology, is in conformity with the general laws of protozoan and bacterial infections.

DISCUSSION.

We consider that the general behavior of this strain of amœbic dysentery will prove to be typical of this species and that *Entamœba histolytica* will conform to the general rules of parasitology in regard to the subinoculation of a susceptible species of animals, especially with regard to the retention of virulence, through at least a moderate number of passages.

There is not sufficient evidence for the view which is generally expressed in the literature to the effect that the subinoculation of a strain of amœbic dysentery is definitely self-limited to a few passages. This self-limitation is ascribed to loss of virulence and changes in the morphology of the entamœbæ. Exactly the opposite result was obtained in the eleven passages which were secured with the strain reported in this paper. It is possible, however, to correlate these contradictory results. The following factors suggest themselves for consideration:

1. Some of the strains which were supposed to be self-limited may have been lost on account of the virulence of the accompanying bacteria.

2. The virulence of the entamœbæ may have been lost by re-inoculating late in the course of the infection of a given individual rather than at the first onset of symptoms.

3. Rectal injections of trophozoites have proven definitely less effective than direct inoculation through the wall of the cæcum into the lumen.

4. The degenerative changes in morphology of entamœbæ which have been described can be explained in part by the (a) long period which the specimens may have remained in the bowel before they were examined and by (b) the comparatively late stages of infection at which the specimens were selected. In view of these considerations, we feel that the previous failures were due to accident, and not to any inherent changes occurring in the entamœbæ upon subinoculation.

PROTOCOLS OF ANIMALS USED.

FIRST PASSAGE.

Oct. 6. Cat I. $\frac{1}{4}$ grown. Intracæcal injection with stools from patient. Oct. 11: Typical dysentery with many amœbæ. Oct. 15: Sick; continued bloody stools. Sacrificed: Gut normal except the rectum which was filled with bloody mucus; no gross ulceration present.

SECOND PASSAGE.

Oct. 15. Cat II. $\frac{1}{2}$ grown. Intracæcal injection from Cat V. Oct. 21: Typical dysentery with many amœbæ. From Oct. 21 to Nov. 7 stools soft, no mucus, blood or amœbæ. Nov. 7: Typical bloody mucous stools with many amœbæ. Nov. 29: Coma; death. Autopsy: Large intestine showed diffuse inflammation with many motile amœbæ. Large liver abscess.

Oct. 15. Cat III. $\frac{1}{2}$ grown. Intracæcal injection from Cat V. Oct. 21: Bloody and mucous stool. Oct. 21 to Nov. 7: Stools soft; no mucus, blood nor amœbæ. Nov. 7: Bloody mucous stools with amœbæ. Nov. 16: Death. Autopsy: Slight subcutaneous infection. Circumscribed ulceration with blood in lower 2 inches of large intestine. Blood culture from heart positive.

THIRD PASSAGE.

Oct. 21. Cat IV. $\frac{1}{2}$ grown. Intracæcal injection from Cats II and III. Oct. 27: Typical dysenteric stools with many amœbæ; continued until death. Oct. 31: Died. Autopsy: Ulceration of lower end of colon with mucus and blood containing active amœbæ. Blood culture positive.

FOURTH PASSAGE.

Oct. 27. Cat V. $\frac{1}{2}$ grown. Intracæcal injection from Cat IV. Nov. 1: Died suddenly. Autopsy: Entirely negative. Blood culture (heart) positive.

Oct. 27. Cat VI. $\frac{1}{2}$ grown. Intracæcal injection from Cat IV. Oct. 31: Died. Autopsy: Negative except for few amœbæ found in stained preparation of rectal contents. Blood culture (heart) positive.

Oct. 28. Cat VII. Adult. Intracæcal injection from Cat IV. Nov. 5: Died. Autopsy: General peritonitis.

Oct. 31. Cat VIII. Intracæcal injection from Cat IV. Nov. 7: Died. Autopsy: General peritonitis.

Oct. 31. Cat IX. Rectal tube injection from Cat IV. Nov. 6: Typical dysentery with blood and mucous stools and many amœbæ. Nov. 7: Sacrificed. Autopsy: Lower colon and rectum filled with bloody mucus containing many amœbæ. Blood culture (heart) positive.

Oct. 31. Cat X. Rectal tube injection from Cat IV. Nov. 7: Blood and mucous stool. This cleared up and animal remained perfectly well until sacrificed in February. Feb. 2: Sacrificed. Autopsy: Entirely negative.

FIFTH PASSAGE.

Nov. 7. Cat XI. Adult. Intracæcal injection from Cat IX. Nov. 10: Sacrificed. General peritonitis.

Oct. 7. Cat XII. $\frac{1}{4}$ grown. Intracæcal injection from Cat IX. Nov. 12: Typical dysentery with blood, mucus and numerous amœbæ in stools; continued until death. Nov. 16: Died. Autopsy: Marked swelling, thickening and ulceration of lower 3 in. of large bowel. Contents consist of blood and mucus with innumerable amœbæ. Blood culture (heart) positive.

Nov. 7. Cat XIII. $\frac{1}{2}$ grown. Rectal tube injection from Cat IX. Nov. 11: Typical dysentery with many amœbæ. Nov. 12: Died. Autopsy: No gross lesions in bowel. Contents consisted of blood and mucus with many amœbæ.

SIXTH PASSAGE.

Nov. 12. Cat XIV. $\frac{1}{2}$ grown. Intracæcal injection from Cat XII. Nov. 17: Typical stools with few amœbæ. No further symptoms noted. Jan. 18: Died. No autopsy.

Nov. 12. Cat XV. $\frac{1}{2}$ grown. Intracæcal injection from Cat XII. Nov. 16: Died. Autopsy: Extensive subcutaneous abscess: general peritonitis.

Nov. 12. Cat XVI. $\frac{3}{4}$ grown. Rectal tube injection from Cat XII. Similar injection repeated on Nov. 13. No symptoms noted, no amœbæ found. Died in January. Autopsy negative.

Nov. 16. Cat XVII. $\frac{1}{2}$ grown. Rectal tube injection from Cat XII. Nov. 19: Typical dysenteric stools with many amœbæ; continued until Nov. 25. Dec. 12: Autopsy: Colon negative; purulent pericarditis and empyema.

Nov. 16. Cat XVIII. $\frac{1}{4}$ grown. Rectal tube injection from Cat XII. Nov. 19: Typical dysentery with many amœbæ. Nov. 20: Died. Autopsy: Thickening and ulceration in rectum. Blood culture (heart) positive.

Nov. 16. Cat XIX. $\frac{1}{2}$ grown. Intracæcal injection from Cat XII. Nov. 17: Died. Autopsy: General peritonitis.

Nov. 16. Cat XX. $\frac{1}{4}$ grown. Intracæcal injection from Cat XII. Nov. 17: Died. Autopsy: General peritonitis; colon contains mucus and slight amount of blood with many amœbæ.

SEVENTH PASSAGE.

Nov. 17. Cat XXI. $\frac{1}{8}$ grown. Rectal tube injection from Cat XX. Nov. 20: Typical dysentery with amœbæ. Died in late afternoon. Autopsy negative. Blood culture positive.

Nov. 19. Cat XXII. $\frac{1}{8}$ grown. Rectal tube injection from Cat XVIII. Dec. 8: No dysentery nor amœbæ. Died. Autopsy negative.

Nov. 19. Cat XXIII. $\frac{1}{8}$ grown. Rectal tube injection from Cat XVII. Nov. 22: Typical dysentery with many amœbæ. Nov. 23: Killed. Superficial ulceration over rectal mucosa with many amœbæ. Blood culture negative.

Nov. 19. Cat XXIV. Adult. Rectal tube injection from Cat XVII. Dec. 8: Typical dysentery with many amœbæ. Jan. 14: Died. Autopsy negative.

EIGHTH PASSAGE.

Nov. 23. Cat XXV. $\frac{1}{8}$ grown. Rectal tube injection from Cat XXIII. Nov. 26: Typical dysentery with active amœbæ. Amœbæ very large size. Nov. 27: Died. Autopsy: Rectal ampulla injected and filled with bloody mucus containing many amœbæ.

Nov. 23. Cat XXVI. $\frac{1}{8}$ grown. Rectal tube injection from Cat XXIII. Nov. 26: Dysentery with amœbæ. Dec. 2: Died. Autopsy: Rectum hyperæmic with ulceration. Contents showed very numerous amœbæ.

Nov. 23. Cat XXVII. $\frac{1}{4}$ grown. Rectal tube injection from Cat XXIII. Nov. 26: Animal is distinctly sick—no stool examination recorded. Dec. 1: Died. Autopsy: Marked injection with swollen granulomatous ulceration of mucosa in region of sigmoid and

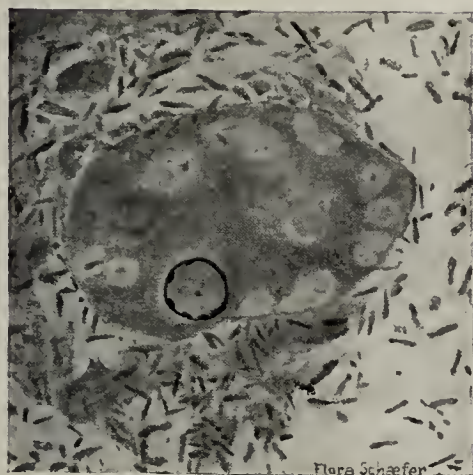


FIG. 1.



FIG. 2.

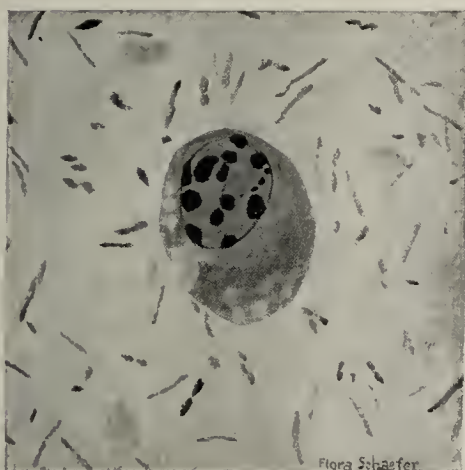


FIG. 3.

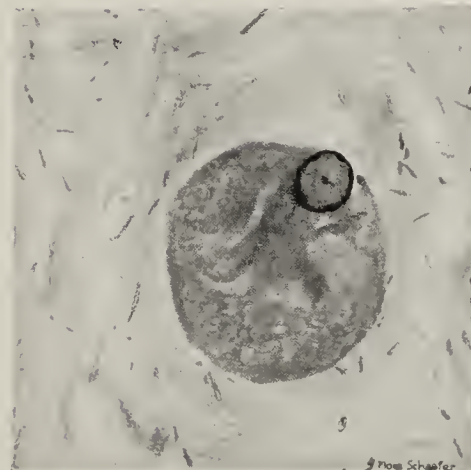


FIG. 4.

especially over the rectum. Contents showed many typical amœbæ. Blood culture positive.

NINTH PASSAGE.

Nov. 27. Cat XXVIII. $\frac{1}{4}$ grown. Rectal tube injection from Cat XXV. Dec. 6: Animal sick; stools contain numerous active amœbæ. Sacrificed. Colon contents in cæcal region contained much pus and active amœbæ. Mucosa of rectum injected and swollen, no ulceration; contents here contain blood and mucus with numerous amœbæ. Blood cultures positive.

Dec. 1. Cat XXIX. $\frac{3}{4}$ grown. Rectal tube injection from Cat XXVII. Dec. 16: Bloody stools. Dec. 26: Distinctly sick; numerous bloody stools. Dec. 28: Died. Autopsy: Slight hyperæmia of rectal mucosa; contents of bowel here are bloody. No microscopic examination for amœbæ noted.

TENTH PASSAGE.

Dec. 6. Cat XXX. $\frac{1}{4}$ grown. Rectal tube injection from Cat XXVIII. Dec. 14: Found dead. Autopsy: Colon hyperæmic with swollen granulomatous appearance over rectal mucosa. Numerous dead amœbæ.

Dec. 6. Cat XXXI. $\frac{1}{4}$ grown. Rectal tube injection from Cat XXVIII. Dec. 26: Typical dysenteric stools. Dec. 28: Died. Autopsy: Slight hyperæmia of rectum; no ulceration.

ELEVENTH PASSAGE.

Dec. 11. Cat XXXII. $\frac{1}{8}$ grown. Rectal tube injection from Cat XXX. Dec. 19: Dysenteric stools containing many amœbæ. Dec.

22: Typical stools containing many amœbæ. Sacrificed. Autopsy: Hyperæmia and swelling of rectal mucosa. Contents of gut at this point showed mucus and blood with many typical and actively motile amœbæ.

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EXPLANATION OF TROPHOZOITES IN PLATE.

(Magnification, $\times 1500$.)

FIG. 1.—From the stool of the patient.

FIG. 2.—From the eleventh passage in animals.

FIGS. 3 and 4.—Degenerating forms from the second passage from a fresh stool, obtained on the third day after the onset of symptoms.

THE BLOOD-PICTURE IN HODGKIN'S DISEASE.¹

SECOND PAPER.

By C. H. BUNTING, M. D.

(From the Pathological Laboratory of the University of Wisconsin.)

In an earlier paper² on Hodgkin's disease, I pointed out characteristics in the blood-picture which seemed at that time to warrant the conclusion that the diagnosis of the disease might be made from blood smears with a considerable degree of accuracy. The earlier paper was based on a study of 11 cases, in all but one of which the diagnosis was established by microscopical examination of a test-gland; and in the one exception, the clinical picture and the course of the disease left no doubt as to the diagnosis.

During the past year it has been possible, through the courtesy of friends in the medical profession, to study the blood of 14 additional cases, in which the diagnosis has been established by the histological examination of a test gland. It has thus been possible to confirm and strengthen the earlier findings.

The series of cases studied includes 15 males and 10 females, a somewhat higher percentage of the latter sex than is usually given. It is further rather striking, that the great

majority of the males are under the thirty-third year, while the majority of the females are above that age.

The study of the blood in these cases has shown, as indicated by the tabulated results, that there is a deviation from the normal leukocytic picture in all cases, but that there is not a single constant picture found in them. Instead, it is possible to divide the cases into two distinct groups according to the differential count of the leukocytes. The first group, including cases of a year or less in duration, shows a normal or slightly increased total leukocyte count with a normal or decreased percentage of polymorphonuclear neutrophils. The second group includes the cases of greater duration for the most part, and shows a sharp leukocytosis, running in one case (as far as could be determined from the smear ratio of 1 white cell to 29 red cells), to at least 100,000 leukocytes per cmm. This leukocytosis is accompanied by an increase of the neutrophils to a percentage between 72 and 90—a percentage ordinarily considered of value in diagnosing a suppurative process in the body, yet occurring in Hodgkin's disease in the complete absence of pus formation.

The explanation of this change in blood-picture is not en-

¹ This work has been aided by a grant from the Rockefeller Institute of Medical Research, New York.

² Johns Hopkins Hosp. Bull., 1911, XXII, 369.

GROUP ONE.											
Case No.	Sex.	Age.	Appar. dura- tion.	Leuko- cyte count.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I	M.	21	4 mos.	7,500	51.2	3.2	1.6	25.4	10	8.6
II	M.	10	1 yr.	9,500	56.2	8.6	5.4	16.4	7.4	11
IV	F.	40	9 mos.	36.	0.6	0.2	39.2	10.6	2.8	10.6
V	M.	8	5 mos.	9,900	59.4	4.6	0.4	21.8	3.6	10.2
VII	F.	64	3 mos.	4,480	54.8	4.2	0.4	20	9.8	1.6	9.2
IX	M.	5	5 mos.	4,200	54.4	2.4	0.2	22.6	8.6	2.4	9.4
XIII	M.	31	14 mos.	6,000	44.8	4.6	0.4	19.4	13.4	2.4	15.0
XVIII	M.	33	6 mos.	64.2	0.4	0.0	16.4	9.2	0.6	9.2
XXI	M.	33	5 mos.	46.8	0.6	1.4	33.4	3.8	0.4	13.6
XXI	M.	37	18 mos.	low	70.4*	1.8	0.4	10.6	3.6	0.0	13.2
XXIII	M.	17	?	10,000	60.4	2	0.6	20.8	6.2	0.2	9.8

* Count taken with recent surgical incision still unhealed.

GROUP TWO.											
III	M.	30	*	10,000	79.4	0.2	0.4	5.8	3.4	10.8
VI	M.	16	?	18,000	81.6	0.6	0.4	4.2	3.	1.6	8.6
VIII	M.	33	76.2	1.4	0.6	7.6	6.	8.2
X	M.	14,300	84.	0.0	0.0	3.8	1.0	1.0	10.2
XI	M.	22	1 yr.	81.8	0.2	0.6	2.6	2.6	1.0	11.2
XII	F.	33	1 yr.	19,000	85.4	2.8	0.0	3.2	0.4	0.2	8.
XIV	F.	52	2 yrs.	100,000	89.2	0.0	0.0	2.4	1.0	0.6	4.
XV	F.	20	1 yr.	9,000	84.4	1.2	0.0	2.2	4.2	0.4	7.6
XVI	F.	34	†	12,400	85.8	0.2	0.4	4.4	3.2	0.6	5.4
XVII	F.	38	2 yrs.	22,000	82.6	2.	0.0	5.2	2.4	0.0	7.8
XV	F.	24	1 yr.	20,000	90.4	0.4	0.0	2.4	1.4	0.0	5.4
XXII	F.	22	2 yrs.	6,200	78.	2.6	1.2	4.4	0.2	0.0	13.6
XXIV	M.	27	7 mos.	44,000	84.	1.6	0.0	8.8	0.4	0.2	5.
XXV†	F.	17	4 mos.	12,000	72.6	0.9	0.4	15.3	3.0	0.4	7.4

* Over 1 year.

† 10 months. (?)

N. = Neutrophile, E. = Eosinophile, B. = Basophile, S. L. = Small Lymphocyte, L. L. = Large Lymphocyte, L. M. = Large Mononuclear, Tr. = Transitional.
† Case XXV was apparently counted in a transition from the early to the late blood-picture. Later counts show an increase in neutrophils to 78.4% and a decrease in lymphocytes to 7.6%.

tirely clear. While the primary blood-picture is usually found in cases of relatively short duration, and with comparatively localized lesions, there are enough exceptions in the series to indicate that these are not the sole factors. If it were possible to examine every gland in every case one might find a pathological explanation for the change. Glands from two of the cases with the sharpest leukocytosis indicated that in these the disease was progressing more intensely. There was more necrosis and a marked infiltration of the gland and surrounding tissue with neutrophile leukocytes. As a result of the bacteriological investigations of Dr. Yates and myself,³ I was on the point of accepting the possibility that complicating infection with staphylococci might be responsible for this increased intensity of reaction when cultures from several glands in a very recent case with such a picture gave only the diphtheroid organism. Inoculation of monkeys with the diphtheroid organism has produced the primary blood-picture, with a slight tendency toward the secondary picture in one monkey, inoculated with an organism of increased virulence. Pathological study of these experimental lesions indicates strongly that while necrosis of lymphocytes leads to chemotaxis for eosinophiles, the necrosis of the proliferated endothelioid cells and fibroblasts leads to positive chemotaxis for neutrophiles. Thus, in the cases with greater intensity of the process, we have the neutrophile leukocytosis.

Turning to the other changes in the differential count, the most striking feature, as indicated in the earlier paper, is the increase in the so-called transitional leukocyte—the large

mononuclear cell with indented or lobed nucleus, abundant protoplasm and fine azurophile granulation with Wright's stain. These cells are absolutely increased in all cases, and relatively increased in all except those with well marked leukocytosis; and even in these latter cases the transitionals are the most numerous cells except the neutrophiles. Thus, in the group of cases with the primary picture, one finds the percentage varying from 8.6 to 15, as opposed to a normal of 7.5; while in the secondary group, the percentage is above normal excepting in four cases with a relatively sharp leukocytosis, and in these it varies from 4 to 5.4. There seems every evidence from blood counts and gland sections in a variety of conditions that these cells are derived from the cells of the germinal centers of lymphoid tissue, and from cells lying upon the reticulum of the lymph cords, and not from the endothelial lining of the lymph sinuses.

The lymphocytes, except for a moderate increase during the first few months of the disease (35.4, 37.2, 49.8 per cent), show a gradual percentage diminution, until in the later cases they vary from 7.6 to 3.4. Apparently the toxin active in the disease, in small doses, leads to a stimulation of lymphocyte production, but in large doses leads to their destruction.

The circulating eosinophile cells show quite a variation in number in the different cases. This seems to depend chiefly upon the reactive power of the marrow. The chemotactic substance which attracts the eosinophile to the glands appears to be some product resulting from the destruction of lymphocytes. Even in the early phase, when this destruction is relatively slight, and there is chiefly proliferation of lymphocytes, the normal marrow does not seem able to compensate and there is a circulatory deficiency. Later, in the well established cases, even with greater demands, marrow compensation is usually excessive, and there is a moderate eosinophilia. In exceptional cases there may be an extreme eosinophilia as shown by a blood smear sent me from the medical laboratory of the Johns Hopkins Hospital, in which there was 68 per cent of eosinophiles in a count of 20,000, and as seen in Case XII of this series, in whom on one occasion there was 33 per cent of eosinophiles in a count of 30,000 leukocytes. In the latter case a rather marked skin reaction to the X-ray may have accounted for the increase.

The basophiles are increased in very early cases, but later almost disappear from the circulation. Basophiles, as well as eosinophiles, may be found in smears from the lymph glands in Hodgkin's disease. This, taken with the blood counts in monkeys inoculated with the diphtheroid organism, suggests that the basophile reaction is specific. However, basophiles appear to be constantly increased in chronic nasopharyngeal and nasal sinus infections, and it may be that such infections in conjunction with the primary lesion of the disease, lead to the early increase in Hodgkin's disease.

In all cases the great increase in blood platelets, noted in the earlier paper, has been found, and with the increase there are always abnormally large platelet masses and pseudopodia.

One may summarize the blood finding then as follows: throughout the disease there are two constant features, an

³ Arch. Int. Med., 1913, XII, 236.

increase in blood platelets and an absolute increase in the transitional leukocytes. In regard to the other elements, in early cases there is a transitory increase in lymphocytes and basophiles, and a deficiency in eosinophiles, with a normal or low neutrophile count, followed by a gradual decrease in lymphocytes and a moderate eosinophilia. In late cases there is a marked neutrophile leukocytosis, and a diminution in percentage of all other elements except the transitional leukocyte.

All of these features of the blood picture in Hodgkin's disease have been reproduced in the monkey following inoculation with the diphtheroid organism isolated from cases of the disease. One finds, as shown by the counts from one monkey here given, the prompt increase in the transitionals and basophiles, the early deficiency in eosinophiles followed by an eosinophilia, and the early stimulation of the lymphocytes, followed by a gradual reduction. The counts are as follows:

Date.	Total count.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
April 15	22,300	51.0	2.4	0.2	40.8	2.8	0.4	2.4
19	Inoculation							
21	17,600	45.4	1.0	0.8	38.2	5.2	0.6	5.8
24	14,000	28.2	1.6	1.2	56.0	5.2	0.6	7.2
May 1	31,250	62.0	1.8	0.4	27.2	2.2	0.4	6.0
23	20,000	42.8	2.2	0.8	46.0	2.2	1.0	5.0
24	Inoculation							
28	34.4	5.0	0.0	49.6	1.8	0.4	8.8
June 7	Inoculation							
11	14,000	29.8	5.4	0.2	54.8	4.6	5.2	7.0
21	Inoculation							
30	50.0	1.8	0.0	38.0	2.0	0.2	8.0
30	Inoculation							
July 1	51.8	2.2	0.2	37.2	2.0	0.2	6.4
2	48.6	3.8	0.2	36.2	3.6	0.4	7.2
3	51.2	1.6	0.2	35.	3.2	0.2	8.6
5	24,000	52.8	2.4	0.0	32.	4.6	0.4	7.8

A gland, removed after the last count recorded, showed many mitoses in endothelioid cells, apparently accounting for the circulatory increase in transitionals. There was also well-marked cosinophilic infiltration, and a lessened production of lymphocytes.

From the foregoing it may be seen that there are sharply marked blood changes in Hodgkin's disease. The question naturally arises: are they of value in diagnosis of doubtful cases? It is my belief that given a case with chronic glandular enlargement and without any suppurative process, and the blood picture which I have designated as the late or secondary, the diagnosis is established. Given the chronic glandular enlargement and the primary blood picture, diagnosis is somewhat more difficult, but, in my experience, can in the great majority of cases be made with certainty. The diagnosis usually lies between Hodgkin's disease and tuberculosis. There are apparently two distinct pictures in tuberculosis of the glands—that found before there is any softening and abscess formation in the glands, and that found when such a change has occurred. The primary picture here is quite distinctive; the secondary picture is more like the early Hodgkin's picture, but the clinical examination in such a case would determine the abscess formation.

The blood counts which I have made in cases of tuberculosis of the glands are as follows:

CASES WITHOUT ABSCESS FORMATION.

Cases.	Total count.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
I	56.	1.8	0.2	26.4	5.	3.	7.6
II	61.8	1.8	0.2	19.4	6.	1.	6.4
III	7,200	59.8	0.2	0.2	31.	1.4	0.0	7.4
IV	10,000	58.	0.6	0.2	33.	2.2	0.0	6.0
V	61.2	0.6	0.2	28.6.	1.8	0.8	6.0
VI	5,000	46.4	1.4	0.2	45.2	1.4	0.0	5.4
VII	61.6	1.2	0.2	20.2	9.	0.6	7.2
VIII	9,400	57.6	1.2	0.6	28.	7.4	0.4	4.8

CASES WITH ABSCESS FORMATION.

I	9,000	41.6	2.4	0.0	43.2	4.4	0.4	8.
II	63.	1.2	0.6	19.	6.	2.2	8.
III	11,000	68.6	3.6	0.2	12.4	6.6	0.6	7.6
IV	53.4	4.2	0.6	26.	7.6	0.2	8.
V	10,800	64.6	5.4	0.2	21.6	0.8	0.8	6.6

The quite constant low eosinophile count associated with a low transitional count in the primary group of tuberculosis cases is in definite contrast to the picture in Hodgkin's disease. In addition, while platelets are usually increased in tuberculosis, one seldom finds so great an increase as in Hodgkin's disease, and the abnormally large platelet masses are, in my experience, lacking in the tuberculosis picture. With the exercise of judgment, therefore, the diagnosis may be made from the blood smear.

One case has thrown some doubt on the possibility of diagnosing between Hodgkin's disease and some forms of the so-called malignant lymphomata. In this case, with a primary orbital tumor of slight greenish cast, and general glandular and splenic enlargement, the blood-picture could not be distinguished from that of Hodgkin's disease. Two counts in that case made at an interval of nine months are as follows:

N.	E.	B.	S.L.	L.L.	L.M.	Tr.
54.6	0.9	0.9	23.3	8.2	0.4	11.5
61.4	0.4	0.8	20.6	3.2	0.4	13.2

This finding may not invalidate the blood picture in Hodgkin's disease. It may, when taken with the fact that there was isolated from this case an organism similar to, if not identical with, that obtained constantly in Hodgkin's disease, explain the difficulty of morphologists in drawing a sharp line between the various forms of apparently malignant glandular hyperplasia.

Abstracts of the Hodgkin's disease cases, upon which this report is based, follow:

CASE I (Dr. Yates).—November 20, 1908. Male, white, 21. Onset of disease, July, 1908. Cervical and axillary glands involved. Test gland removed October 30, 1908, showed early Hodgkin's changes. Gradual improvement under treatment. Clinically well since June, 1909, except for some nasal infection.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XI. 20, '08.....	5,304,000	7,500	51.2	3.2	1.6	25.4	10.		8.6
III. 4, '09.....	4,968,000	4,800	55.2	2.4	0.8	23.6	6.6		11.4
VI. 11, '09.....	5,600,000	7,000	65.8	2.8	0.0	16.8	7.6	1.2	5.8
II. 16, '10.....	5,800,000	7,000	59.8	4.0	1.4	15.4	8.8	1.8	8.8
VI. 9, '11.....	8,500	65.0	2.6	1.2	21.2	3.	0.6	6.4
IV. 17, '12.....	5,000	42.2	5.8	0.6	41.4	1.8	0.4	7.8
XI. 17, '13.....	10,000	60.	2.6	0.8	27.4	3.8	0.2	5.2

CASE II (Dr. Yates).—Male, white, 10. Large mass of discrete glands in left cervical region of at least one year's duration previous to removal, November 10, 1908. Glands show well-marked Hodgkin's picture. Von Pirquet reaction negative October 8, 1910.

Gradual improvement under treatment. Increase in size of one gland left at first operation in March, 1913. Removed. Apparently well—1914.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
IV. 1, '09.....	4,712,000	9,500	56.2	8.6	0.4	16.4	7.4	11.0	
I. 22, '10.....	5,250,000	9,600	63.6	3.6	0.0	12.0		6.8	
III. 12, '10.....			53.4	5.2	1.0	13.	16.	1.6	9.8
X. 8, '10.....	4,960,000	9,800	53.2	5.2	0.4	27.8	4.	1.4	8.0
II. 13, '12.....		8,000	57.	4.4	0.2	27.4	4.	0.2	6.8
VI. 3, '12.....	5,500,000	7,000	64.	4.	0.2	19.8	3.2	0.2	8.4
III. 10, '13.....			39.6	10.4	0.6	25.	10.4	1.0	13.0
IX. 18, '13.....			64.2	3.6	0.6	22.	1.8	0.0	7.8

NOTE.—Recurrence found after paper was in press, associated with return of blood picture to that noted earlier during active stage of the disease.

CASE III.—April 1, 1909. Male, white, 30. Seen 2 weeks after second operation for glands of neck. First operation 6 months previous at Rochester. Diagnosis, Hodgkin's disease.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
IV. 1, '09.....	4,560,000	10,000	79.4	0.2	0.4	5.8		3.4	10.8

CASE IV (Dr. Tupper, Eau Claire, Wis.).—February 5, 1910. Female, white, 40. Onset, — months previous in right inguinal glands. Subsequent involvement of left inguinal, left axillary, left and right cervical glands. Test gland shows well-marked active Hodgkin's picture. Death in October, 1910.

BLOOD COUNTS.

Date.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
II. 5, '10.....	36.	0.6	0.2	39.2	10.6	2.8	10.6

CASE V (Dr. Yates).—November 9, 1909. Male, white, 8 years. Enlargement of cervical glands began 5 months previous to date. Left inguinal glands also enlarged. Test gland, November 30, 1909, shows hyperplastic stage of lesion. January, 1910, cervical glands removed. October, 1910, von Pirquet test negative. April, 1911, mucous membrane hæmorrhages, anæmia. Died January 10, 1912. Involvement of mesenteric glands, chylous ascites, wasting.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XI. 9, '09.....		9,900	59.4	4.6	0.4	21.8		3.6	10.2
XI. 30, '09.....			50.8	5.8	0.6	26.8		7.2	8.8
II. 26, '10.....	5,000,000	5,000	55.2	1.4	0.4	22.4	9.2	2.0	9.4
IX. 7, '10.....	5,160,000	8,700	59.4	1.	1.2	16.4	6.6	5.	10.4
IV. 21, '11.....	3,456,000	4,800	63.2	1.8	1.	10.2	4.6	1.4	17.8

Transfused.									
IV. 24, '11.....	3,176,000	3,800	54.	6.8	0.2	17.8	4.8	1.8	14.6
V. 2, '12.....	2,624,000	8,300	67.6	1.4	1.4	6.8	9.6	0.6	12.6

Transfused.									
V. 5, '11.....	2,760,000	4,500	54.6	2.6	2.	18.8	7.6	0.6	13.8
V. 9, '11.....	3,200,000	4,000	50.8	4.	1.6	25.8	6.4	0.6	10.8

Transfused.									
V. 10, '11.....			60.	9.8	0.6	8.2	6.8	0.4	14.2
V. 13, '11.....	3,400,000	3,500	56.2	4.8	0.8	17.6	6.4	0.4	13.8
V. 22, '11.....	3,712,000	3,400	55.8	3.2	0.0	19.8	3.6	1.2	16.4
V. 29, '11.....	3,680,000	3,600	56.4	3.4	1.6	18.	8.1	0.6	11.8

CASE VI (Dr. Sullivan, Madison, Wis.).—March 1, 1910. Male, white, 16. Left cervical glands much enlarged. Marked induration of neck. Enlargement noted for only 1 month, but the amount of sclerosis in test gland suggests greater duration. March 10, wound resulting from removal of gland for diagnosis still unhealed. May 13, wound healed but induration of neck marked. Death during 1911.

BLOOD COUNTS.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
III. 10, '10.....	18,000	81.6	0.6	0.4	4.2	3.	1.6	8.6
V. 13, '10.....	27,000	80.6	1.6	0.0	7.8	2.8	0.8	6.4

CASE VII (Dr. Bennett, Oregon, Wis.).—January 5, 1910. Female, white, 64. In October, 1909, general glandular enlargement with clinical diagnosis of Hodgkin's disease. Death June 30, 1910.

BLOOD COUNTS.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
X. 24, '09.....	3,200,000	4,480							
I. 5, '10.....			54.8	4.2	0.4	20.0	9.8	1.6	9.2

CASE VIII (Dr. Yates).—Male, white, 33. Onset in March, 1907, with supraclavicular glandular enlargement. In September, 1908, supraclavicular and left axillary glands most enlarged. Some

enlargement of right cervical, axillary and inguinal glands. October 30, 1908, excised gland shows typical and advanced Hodgkin's disease. Death occurred May 20, 1909.

BLOOD COUNT.

Date.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I. 10, '09.....	76.2	1.4	0.6	7.6		6.0	8.2

CASE IX (Dr. Yates).—October 3, 1910. Male, white, 5. Marked enlargement of left cervical glands of 5 months duration. Test gland shows well marked Hodgkin's changes. Death from shock at operation.

BLOOD COUNT.

Date.	R. b. c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
X. 3, '10.....	5,160,000	4,200	54.4	2.4	0.2	22.6	8.6	2.4	9.4

CASE X (Dr. Yates).—Male, white, cervical Hodgkin's. Count made 2 months previous to death of patient.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
IV. 30, '10.....	14,300	84.	0.0	0.0	3.8	1.0	1.0	10.2

CASE XI (Dr. Baird, Eau Claire, Wis.).—December 8, 1910. Male, white, 22. Enlargement of supraclavicular gland noted one year previous. Axillary glands enlarged at date. Test gland shows definite Hodgkin's picture.

BLOOD COUNT.

Date.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 8, '10.....	81.8	0.2	0.6	2.6	2.6	1.	11.2

CASE XII (Dr. Yates).—Female, white, 33. October, 1911. Enlargement of the right cervical and axillary glands of one year's duration. Test gland showed a picture of advanced typical Hodgkin's disease. Cervical glands removed February 13, 1912. Subsequent X-ray treatment. Removal of recurrences in right axilla and left sub-clavicular region January, 1913; March, 1913; July, 1913. Clinically well 1914.

BLOOD COUNTS.

Date.	W. b. c.	N.	E.	B.	S. L.	L. L.	L. M.	Tr.
IX. 27, '11....	19,000	85.4	2.8	0.0	3.2	0.4	0.2	8.0
X. 3, '11....	21,000	72.4	11.0	0.2	5.6	2.2	0.2	8.4
X. 31, '11....		73.8	6.2	0.8	7.6	2.5	0.6	8.2
XII. 1, '11....	35,000	84.	2.9	1.1	4.7	0.9	0.1	6.3
XII. 29, '11....	21,000	72.	11.0	0.4	9.2	0.9	0.0	5.5
II. 13, '12....		74.2	9.2	0.2	9.2	1.2	0.0	6.0
III. 15, '12....	30,000	48.0	36.	1.4	9.0	1.2	0.0	4.4
IV. 10, '12 ..	17,000	73.2	10.	0.6	7.2	0.6	0.0	8.4
V. 3, '12....	17,000	74.2	9.6	0.2	10.8	1.4	0.0	3.6
VI. 1, '12....	12,500	77.8	7.4	0.8	8.8	0.0	0.2	5.0
X. 8, '12....	16,000	70.	12.6	0.0	8.6	1.8	0.2	7.0
XI. 27, '12....	15,000	72.6	8.6	0.4	7.4	3.4	0.0	7.6
I. 11, '13....	16,000	80.3	5.0	0.1	4.2	2.6	0.2	7.6
II. 14, '13....	13,000	71.8	12.2	1.0	7.4	1.4	0.0	6.2
III. 3, '13....	15,500	64.8	13.2	0.6	12.4	3.2	0.0	5.8
IV. 12, '13....	15,000	74.	6.8	1.0	10.0	0.8	0.0	7.4
VII. 14, '13....	15,000	71.	8.8	1.8	10.6	1.6	0.0	6.2
VIII. 4, '13....	7,000	51.0	10.0	0.0	27.0	0.8	0.2	11.0
I. 22, '14....	11,000	66.0	9.6	0.8	15.0	1.4	0.6	6.6

CASE XIII (Dr. L. F. Barker, Baltimore).—Male, white, 31. Enlargement of cervical glands, right side, of fourteen months duration. Test gland positive.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 23, '12.....	5,700,000	6,000	44.8	4.6	0.4	19.4	13.4	2.4	15.0

CASE XIV (Dr. S. T. Reeves, Albany, Wis.).—Female, white, 50. The glandular swelling had first appeared in the left cervical region two months previous to the patient's death. At the post mortem examination January 15, 1913, there was found rather general glandular involvement, but especial enlargement of the mesenteric and retroperitoneal nodes and of the lymphoid elements of the spleen. There was also a chylous ascites, well marked anemia and emaciation. Leukocyte count estimated from ratio of 1 white cell to 29 red cells.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 27, '12.....	100,000	89.2	0.0	0.0	2.4	1.0	0.6	4.0

CASE XV (Cook County Hospital, Chicago).—Female, white, 20. Marked enlargement of cervical glands; moderate of axillary and inguinal glands. Spleen palpable. Duration fourteen months. Test gland positive.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
II. 18, '12.....	9,000	84.4	1.2	0.0	2.2	4.2	0.4	7.6

CASE XVI (Drs. Mayo, Rochester).—Female, white, 34. Four years previously she noticed a swelling on the right side of her neck, followed by the appearance of other small tumors. Ten months before date enlarged lymph-nodes appeared on the left side of the neck and in the right axilla. Six weeks previously nodes appeared in the left axilla. Physical examination revealed, in addition to these nodules, a mediastinal mass, and a six months' pregnancy, over which were felt discrete firm nodules which slipped under the examining hand. Test gland positive.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I. 9, '13.....	4,480,000	12,400	85.8	0.2	0.4	4.4	3.2	0.6	5.4

CASE XVII (Drs. Mayo, Rochester).—Female, white, 28. Marked enlargement of the cervical nodes and rather general glandular enlargement. The illness began with involvement of the cervical glands two years previous to date. Test gland showed extreme sclerosis with many giant cells and eosinophiles in the meshes.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
II. 15, '13.....	22,000	82.6	2.0	0.0	5.2	2.4	0.0	7.8

CASE XVIII (Drs. Mayo, Rochester).—Male, white, 33. The patient had had an abscess of a tooth six months previously. About three weeks before coming to the hospital patient had noticed a painless swollen node in the left supraclavicular region. This had increased in size during the time of observation. The large node removed was of a uniform medullary appearance on gross section, and microscopically showed lymphoid and endothelial hyperplasia, with the presence of giant cells, beginning diffuse sclerosis and eosinophilic infiltration. The architecture of the node was destroyed.

BLOOD COUNT.

Date.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I. 31, '13.....	64.2	0.4	0.0	16.4	9.2	0.6	9.2

CASE XIX (Dr. Frank Billings, Chicago).—Male, white, 32. Loss of weight since January 1, 1913. Glandular enlargement noted in February, 1913. On examination, in April, moderate enlargement of cervical, axillary and inguinal glands, tonsils and spleen. Abscess of right upper molar found. Gland showed early changes.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
IV. 28, '13.....	4,150,000	4,150							
V. 29, '13.....			46.8	0.6	1.4	33.4	3.8	0.4	13.6

CASE XX (Dr. C. P. Howard, Iowa City).—Female, white, 24. January, 1913. Enlargement of glands of left axilla noted. In February, 1913, glands of right axilla enlarged; also those of both sides of the neck and of the mediastinum. Gland positive.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 8, '13.....	4,780,000	20,000	90.4	0.4	0.0	2.4	1.4	0.0	5.4

CASE XXI (Dr. Yates).—Male, white, 37. Cervical glandular enlargement for twenty-one months. Removal of single glands at various times. Tonsillectomy June, 1913. December, 1913, large group of glands in left side of neck; no other enlargement.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 13, '13.....	Low	70.4	1.8	0.4	10.6	3.6	0.0	13.2

CASE XXII (Dr. G. E. Pfahler, Philadelphia).—Female, white, 22. Cervical glands noted in November, 1911. Subsequent involvement of mediastinal, mesenteric and retroperitoneal glands.

BLOOD COUNT.

Date.	R.b.c.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 10, '13.....	4,420,000	6,200	78.0	2.6	1.2	4.4	0.2	0.0	13.6

CASE XXIII (Dr. H. L. Ulrich, Minneapolis).—Male, white, 17. Operation for glands of the neck at age of 10. Operation at Rochester, November, 1912, for glands of neck. Diagnosis: tuberculosis. Gland removed in 1913; diagnosed at University of Minnesota laboratory as Hodgkin's disease. In December, 1913, enlarged glands in both sides of neck and in right axilla. Test gland shows unmistakable, typical well-developed Hodgkin's disease lesion.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 29, '13.....	10,000	60.4	2.0	0.6	20.8	6.2	0.2	9.8

CASE XXIV (Dr. Yates).—Male, white, 27. Glandular enlargement first noted in May, 1913. Marked enlargement of cervical axillary and mediastinal glands. Marked periglandular inflammation. Test gland shows intense and relatively acute reaction; but typical Hodgkin's disease features.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
XII. 20, '13.....	44,000	84.	1.6	0.0	8.8	0.4	0.2	5.0

CASE XXV (Dr. Yates).—Female, white, 17. Glandular enlargement first noted in September, 1913. Marked involvement of left cervical and axillary regions and of mediastinum. Well-marked periglandular reaction. Sclerosis of excised gland indicates greater duration.

BLOOD COUNT.

Date.	W.b.c.	N.	E.	B.	S.L.	L.L.	L.M.	Tr.
I. 17, '14.....	15,000	72.6	0.9	0.4	15.3	3.0	0.4	7.4

HODGKIN'S DISEASE.¹

By C. H. BUNTING, M. D.

(From the Pathological Laboratory of the University of Wisconsin.)

My interest in Hodgkin's disease dates from a series of experiments performed in the laboratory of Dr. Flexner at the University of Pennsylvania in 1903. In some of these experiments, the intraperitoneal injection of a lymphotoxic

¹ Paper read at a meeting of The Johns Hopkins Hospital Medical Society, Feb. 2, 1914. The work forming the basis of this report has been aided by a grant from the Rockefeller Institute of Medical Research.

serum produced in the mesenteric lymph glands of the rabbits changes which were of the nature of the earliest changes in Hodgkin's disease; that is, there was necrosis of lymphocytes, proliferation of endothelioid cells, infiltration by eosinophiles and a proliferation of fibroblasts independent of the gross framework of the gland.

These results, coupled with the inability of those working on the disease at that time to find pathogenic organisms in

the glands, led to the development of a working theory as to the pathogenesis of Hodgkin's disease which I still hold, though in a modified form. This conception of the disease was, that the changes in the lymph glands were due to the filtration through them of a toxin elaborated at some primary focus of infection, and were in consequence entirely of a secondary nature—an end-result. For the explanation of the progress of the disease, I must introduce a subsidiary theory which seems borne out by pathological and experimental experience, that lymphadenoid tissue affords not only a mechanical, but also a chemical, filter for peripheral lymph, protecting the body cells generally and the red blood cells in particular, from a variety of toxins, at the expense of its lymphocytes. So in Hodgkin's disease, the primary group of glands, for a considerable length of time, protects the body from the toxin elaborated by the infectious agent. The removal of that group of glands by its ultimate sclerosis or by the hand of the surgeon, while the primary focus remains intact, exposes the body to an extension of the process to further glandular groups and, eventually, to an anemia and a cachexia.

This theory slumbered until 1908, when, on my return to Wisconsin, I found that Dr. Yates was deeply interested in the disease, and we decided to join forces in an attempt to unravel its difficulties and to further its treatment. We have been handicapped throughout by the distance between us, and more by our inability to control a sufficient material for study. We have, however, through the kindness of friends in the medical profession, come in contact in one way or another with 28 cases.

From the standpoint of general etiology, the most striking feature of this series is that 13 of the cases were females and 15 males; and further, that while the males were, with but a single exception, under 34 years of age (and the exception but 35 at onset), the ages of 8 of the females ranged from 33 to 64 years. Both of these features are in contrast to Ziegler's² statistics derived from 210 cases gathered from literature. While it is dangerous to draw conclusions from a small series of cases, it would appear equally dangerous to follow Ziegler's method, if I may judge from a single case of which I have knowledge,³ included in his series.

The study of these cases from a pathological standpoint has but strengthened the conviction that the lesion of Hodgkin's disease is essentially of inflammatory nature. The work of Reed and of Longcope leaves practically nothing of importance to be added to the description of the changes within the glands themselves, unless one emphasizes the fact that there are cases in which the disease runs so intense a course that the necrosis and the inflammatory reaction in the glands almost overshadow the more usually accepted chronic Hodgkin's disease picture. This appears to occur without secondary infection as far as cultures can determine.

² Die Hodgkinsche Krankheit, Jena, 1911.

³ Among his cases of Hodgkin's disease of the spleen is included a metastasizing sarcoma of the spleen-pulp, published by me some years ago. In this case there was no involvement of the lymphoid tissue in the spleen or elsewhere.

Aside from the gland lesions there are, however, two points in the pathology of the disease which deserve mention. Careful search will, in the majority of cases, reveal a primary inflammatory lesion which was present before the enlargement of the glands occurred. In primary cervical Hodgkin's disease, this is most apt to be in the tonsils, teeth or nasal sinuses. In one primary cervical case, an otitis media of some duration proved the source of the infection. In a primary inguinal case the physician gave a history of a sharp attack of cystitis preceding the glandular enlargement. However, infection through the gastrointestinal mucous membrane is possible, as shown in cases in which the lesions are confined to the lymphoid tissue of the tract and the mesenteric glands.

The second point I wish to emphasize is that, while the glands in Hodgkin's disease remain discrete, they are, nevertheless, bound together in chronic cases by a mass of sclerotic tissue. In other words, there is in the disease an extraglandular inflammatory process which is of a relatively acute nature in early cases, showing a marked inflammatory oedema and a moderate and diffuse infiltration with polymorphonuclears, as well as with large and small mononuclears. There is an early stimulation of fibroblasts leading to the marked sclerosis of chronic cases.

That there is a general systemic reaction in Hodgkin's disease and not simply a process within a gland or group of glands is indicated by the changes in the blood picture, to which I have given considerable study, but to which I shall refer only briefly here, as I have considered them in detail in another paper.

A study of 25 cases shows that they may be divided into two groups according to their blood picture. The first of these groups includes roughly those cases of less than a year's duration, and the second, those of over a year's duration, although duration does not appear to be the chief factor in determining the blood picture. The blood in both groups shows a marked increase in blood platelets, with the presence of large platelet masses and megalokaryocyte pseudopodia. The only other constant feature is an absolute and usually a relative increase in the so-called transitional cell—the large mononuclear with indented or lobed nucleus and abundant protoplasm with azurophile granulation. This is Mallory's endothelial leukocyte, but I believe it is derived from the cells of the reticulum of lymphoid tissue rather than from the lining of the sinuses.

Except in these two points, the two groups of cases vary in blood picture. The first group shows little, if any, increase in the total leukocyte count; the second, usually a pronounced leukocytosis, even up to 100,000 cells per cmm. In the very early cases of the first group, there is a deficiency in eosinophiles, a slight increase in basophiles, and a fairly well marked lymphocytosis. This is followed after compensation by a slight eosinophilia, and by a gradual decrease in lymphocytes.

In the second group of cases, we have a neutrophile leukocytosis, the percentage of these cells ranging from 76 to 90 in the series. Lymphocytes are exceeded in number by the transitionals in 10 out of 13 cases falling in this group.

Those three may be the only varieties of cells found. The blood picture appears to be of diagnostic value in cases with chronic glandular enlargement; at least, the differentiation from tuberculosis of the glands is possible. I have not been able, however, to differentiate Hodgkin's disease from certain cases of the so-called malignant lymphoma by the blood smear.

In spite of the failure of others to obtain organisms in cultures from cases of Hodgkin's disease, Dr. Yates and I made efforts, wherever opportunity offered, to find by the cultural method the agent producing the disease. Our early efforts at operation and post mortem examination were failures. Our success in obtaining the organism, which we are convinced is the cause of the disease, was, I believe, the result of the following factors: Choice of a suitable medium, the implantation of large pieces of gland tissue with interglandular tissue, and incubation for a sufficiently long period. These steps were not adopted purely by accident. We felt that the organism was one of the so-called higher bacteria, if not a fungus, and consequently, selected cultural material suitable for the growth of the tubercle bacillus; *i. e.*, Dorsett's egg medium and glycerine-phosphate-agar. We further concluded that the organisms were few in number in the glands and were also difficult to grow, so slices of gland as large as the diameter of the test tube would permit were implanted, with the idea that in this way we should stand more chance of implanting organisms, and also with the thought of furnishing sufficient human proteid to give the organism a start at growth. Finally we sealed the tubes and incubated them indefinitely.

Our first successful implantation was made in February, 1912, when, after 10 days' incubation of tissue from a case, we found growth of a diphtheroid organism in 3 of 6 tubes and on both egg medium and glycerine-phosphate-agar. Since then we have not failed to find the organism in any active case of Hodgkin's disease (untreated by the X-ray), in which we have had opportunity to get cultures. It has been found by us, usually in pure culture, in cervical, axillary, and inguinal glands, and in the spleen. However, not infrequently in some tube a growth of a white coccus would be found, although every effort was made to prevent contamination from the skin of the patient operated upon.

The cultural method indicates that even in relatively acute cases the number of organisms in the glands is small. Growth may appear in but 3 or 4 tubes out of a dozen, and in any one tube there are but few colonies.

The organism grows feebly from most cases when first isolated, and may require careful nursing in order to secure a growth upon the medium independent of the human tissue. Two cultures, however, grew very luxuriantly from the start, and one of these we have used for our experimental work. Growth of this culture, however, was as difficult to obtain, after passage through the monkey, as in the majority of human cases.

The organism is Gram-staining and non-acid-fast, and its most striking feature is its pleomorphism. This is so remarkable that about six weeks were spent in an effort to separate supposed contaminations of the culture. The cultures on

different media and at different ages show long, banded, and granular rods, fusiform rods, club shaped and large spherical involution forms, short, plump bacilli with polar staining, and coccoid forms. In the older cultures the coccoid forms predominate. Yet a fresh transfer of such coccoid forms will give, on suitable media, the characteristic, long, diphtheroid bacilli.

While one might not expect that an organism which did not produce death in human beings acutely, would be highly virulent to laboratory animals, yet our early experiments were disappointing. Large doses of 24-hour cultures appeared almost innocuous to guinea pigs and white rats. When recourse was had to the monkey, a similar disappointment was met with. By repeated injections, changes were produced in the lymph glands similar to those found in the glands in early cases of Hodgkin's disease in man. Yet the organism would not gain a foothold, apparently, and the glandular enlargement and the periglandular induration would subside. However, that difficulty was overcome. The first step was the recovery of the organism in pure culture from an abscess developing at the site of an inoculation two days before. This organism was then used for injection of the other monkeys. From one of these monkeys an enlarged gland was removed one week after inoculation in its vicinity, and was implanted subcutaneously into another monkey. This animal died in 10 weeks with marked involvement of its lymphoid tissue. The organism was recovered in pure culture and a small dose was inoculated into a monkey which had proved refractory to the original culture. This monkey died also, within 10 weeks, and with most marked lesions of its lymphoid tissue throughout.

One monkey finally became susceptible to the original culture and has shown progressive glandular enlargement since the last injection in August, 1913. Thus we have demonstrated the pathogenicity of the culture, but its virulence toward the monkey has been increased to such a point that the resulting lesions are of a very acute nature.

The elements of the Hodgkin's disease gland picture are present. One finds the marked proliferation of endothelioid cells, with endothelioid giant-cells, eosinophile infiltration, and a proliferation of fibroblasts. However, these changes are overshadowed by the extensive necrosis of tissue, and the polymorphonuclear leukocyte infiltration of the necrotic areas. These areas appear to be made up chiefly of the newly proliferated endothelioid cells. While this picture may seem quite different from that seen in the more chronic cases in human beings, we have recently had its counterpart in a patient with Hodgkin's disease in whom the course of the disease was of a relatively acute nature.

I have been impressed, also, by the fact that in the monkeys inoculated with the organism of increased virulence, the pathological changes in the lymphoid tissue are in many features strikingly like those described by Councilman, Mallory and Pearce in human cases dying of diphtheria. As a result of these experimental studies, and of the incomplete observation of certain clinical cases, I believe we shall

find that some obscure infections in man resulting in extensive subcutaneous inflammatory reaction without pus formation, and in intense glandular reaction, will be proved, upon bacteriological investigation, to be cases of acute Hodgkin's disease.

There is one other relationship of Hodgkin's disease that needs mention. Morphologically there is great difficulty in diagnosing between various types of so-called malignant lymph gland lesions. As I have mentioned earlier, in a case of malignant lymphoma, with a primary, slightly greenish tumor in the orbit, and with general glandular and splenic enlargement, the blood picture was identical with that in Hodgkin's disease. Furthermore, a culture was obtained from the glands in this case of an organism quite similar to, if not identical with, that obtained from cases of Hodgkin's disease. Billings and Rosenow have also reported the cultivation of a diphtheroid organism from a case diagnosed histologically as lymphosarcoma. In the chloroma case there was noted at operation, also, the same marked interglandular sclerosis seen in Hodgkin's disease. These findings practically force the suggestion, open to further proof or disproof, that these diseases differ but quantitatively and not qualitatively.

To summarize our picture and revise our theory, Hodgkin's disease is an infectious disease due to a diphtheroid organism, the *Bacterium Hodykini*. There may often be found a primary lesion at the portal of entry. While in some cases the organisms may remain for a long time localized in the vicinity of the portal of entry, in other cases they early gain entrance into the general circulation, and may be widely distributed. The organism and its toxin show a special affinity for lymphoid tissue, and produce in this the characteristic changes of Hodgkin's disease, changes varying somewhat according to the intensity of the toxin, but resulting ultimately in the sclerosis of the glands. There is at the same time an interglandular inflammatory process, at times very acute, but resulting finally in a dense sclerotic tissue. There are also characteristic blood changes in the disease.

The glandular changes can then be considered only as the result of a toxic action, and contribute to the patient's death merely incidentally, when certain gland groups are extensively enlarged. The cells of the enlarged glands, though atypical, show none of the antagonism to the other body cells characteristic of malignant neoplasms.

A CLINICAL CONSIDERATION OF HODGKIN'S DISEASE.*

By J. L. YATES, M. D., F. A. C. S., Milwaukee.

This communication is based upon studies made during the last six years in conjunction with Dr. C. H. Bunting, of Madison, Wis., and is to be regarded as both elementary and preliminary in nature.

Definition.—Temporarily Hodgkin's disease may be considered an infectious, non-contagious affection due to the *B. Hodykini*. It is characterized by a somewhat variable, though definite, reaction in the lymphatic and perilymphatic structures, specific changes in the blood picture and by the manifestation of little or no tendency to spontaneous recovery.

Diagnosis.—Heredity and contagion have little, if any, significance in the history. The sexes are equally represented (16 males, 15 females) between five and sixty-four years with an apparent tendency to appear comparatively earlier in males and later in females. As a rule there is disclosed nothing sufficiently definite symptomatically to indicate the time of infection or the portal of entry. Enlargement of the cervical glands is commonly noted as the first evidence of the disease, and is usually discovered by chance during a period of well being. Infrequently this glandular enlargement is preceded by a sense of lassitude, or there may have been a well-defined,

if not severe, irritation in the throat, nose, eye or ear. Glands in the lower posterior cervical triangle are more commonly noted primarily than those higher up, further extension taking place, in order of frequency, to the axilla on the same side, to the opposite cervical region, the mediastinum, the opposite axilla, to the groins and the peritoneum, the spleen and liver. Primary involvement in the inguinal glands has been noted as following cystitis and leucorrhœa or has appeared without the least evidence of any exciting cause (lymphosarcoma?). In acute cases the enlargement of glands first affected, and the subsequent extension to other members of the same group and to other groups of glands may be rapid and rather steadily progressive. Perhaps more often there are alternating periods of enlargement and regression even in the acute type. During the periods of enlargement (this is noticed by the more observing patients) the individual glands seem partially to lose their identity, the whole group becoming fused into a nodular mass. This may lead to boggi-ness in the subcutaneous tissue or even to redness and edema-tous induration in the skin. Excision of tissue and subsequent microscopic study by Dr. Bunting has demonstrated that these changes are due to waves in the acuteness of the periadenitis, rather than to increased adenitis and may have an important bearing upon the question of treatment. Early bad effect upon the general health is attributable to toxæmia which is always sufficient to affect the blood picture. During intervals of regression in the glandular enlargement there is apt to be a sense of greater well being, with a corre-

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sponding sense of lassitude when there is an increased enlargement. Thus it may be suspected that there are waves in the toxin production.

Later appears the secondary anemia due probably to an hemolysin produced by the organism, and rarely, spontaneous recurrent hemorrhages from some of the mucous membranes resulting from an absence of the blood platelets caused by exhaustion of the bone marrow. The Pel-Ebstein type of recurrent fever, seen late in the disease, need not be due to any intercurrent infection and has thus far indicated a hopeless prognosis.

Death may result from grave anemia, cachexia, obstruction to respiration, to the circulation or to pressure upon the thoracic duct with consequent chylous ascites or to a combination of these factors. It is commonly supposed to occur in from a few months after onset to within five years but to be inevitable.

An absolute diagnosis cannot be made without laboratory assistance in the histological and bacteriological examination of the blood and excised tissue. So positive a statement demands some explanation.

Hodgkin's disease may simulate tuberculous adenitis so closely, even to involvement of the preauricular gland that clinically they may be indifferentiable. Lymphatic leukemia, believed by Cohnheim and Wunderlich to be but a stage of pseudoleukemia or Hodgkin's disease, made a transient appearance in the course of one case under our observation, an extremely significant observation, particularly if the organism isolated by Steele* from a lymph gland in that condition should prove to be the *B. Hodgkini*. In one case of chloroma and two cases of lymphosarcoma (clinical and histological) Bunting has diagnosed Hodgkin's disease by a blood count and found confirmation in positive cultures from the excised tissue. Rosenow† obtained the diphtheroid organism from a tissue histologically diagnosed lymphosarcoma.

Complications.—Tuberculosis has been unexpectedly infrequent. In but two instances has there been a positive von Pirquet reaction, one with a limited apical lesion, one (lymphosarcoma) with none demonstrable. One case had secondary lues. Terminal acute infections are perhaps the rule.

Blood.—In spite of Dr. Bunting's work (Johns Hopkins Hosp. Bull., 1911, XXII, 114) on the blood picture in Hodgkin's disease, it is almost universally accepted that there is manifested herein, nothing essentially or constantly characteristic. We have had repeated opportunity in the past six years to test out the accuracy of this observation of Dr. Bunting's and have no hesitation in stating most emphatically that, in his hands at least, a differential blood count is the surest and the quickest method of establishing a diagnosis. During this time repeated attempts have been made to confuse and to confound Dr. Bunting by submitting to him unidentified blood smears from individuals suffering from other maladies with and without adenopathies, and thus far his differentiation of Hodgkin's disease has been correct with but

a single exception and that early in the work and in a case complicated by a terminal intercurrent infection. One cannot overestimate the importance of these blood examinations for by them, as will be shown later, some guide can be found as to the efficacy of the treatment and they afford the only sure way to determine ultimate recovery.

Cultures.—When the specific organism can be isolated, a diagnosis is established, no matter what may be the histological picture of the affected tissue. Until the occurrence of the organism in various borderline affections has been determined and thereby the lesions that it may cause have been recognized, its presence must be accepted, until the specificity of the blood picture is established, as the one irrefutable diagnostic feature.

Excised Tissue.—A diagnosis of Hodgkin's disease from a section showing the changes described by Reed could no longer be questioned. It will be some time before an equally positive diagnosis can be made in sections showing changes long supposed to indicate other affections, *e. g.*, certain types of leukemia, lymphosarcoma or chloroma. For the present negative histological evidence must, to some extent, remain inconclusive.

Attempts are being made to develop some form of a diagnostic skin reaction, but so far the results are too inconstant to be reliable. Specific agglutinins have not been found.

Treatment.—The hopelessness of the disease has seemed to warrant recourse to any therapeutic measures that have promised even temporary relief. On the other hand, we have attempted nothing that appeared irrational in the light of the progress of Dr. Bunting's brilliant and thorough investigations. During four years of futile search for the causative agent, we were misled into blind alleys, but happily none was harmful in results and each taught its invaluable lesson as to those things not to do, some of which will be mentioned to safeguard others. If any progress has been made or is to be made in the treatment of Hodgkin's disease it must be through a rational clinical application of laboratory observations.

Observation of cases over a considerable period has taught that successful treatment is dependent upon unremitting watchfulness, and the forehanded recourse to every precaution to establish and to keep the balance of power on the side of the individual against the virulence of the infection, which, notoriously insidious in its onset and ruthless in its initial progress, is often even more so in recrudescence.

Cases can be classified primarily as favorable or unfavorable upon the basis of the evident relative virulence of infection and by the nature and distribution of involvement, rather than through the extent to which individual groups of glands have become affected. Slower growing glands with a tendency to remain discrete are more favorable even when involving multiple groups, for example, both sides of the neck and an axilla, than those exhibiting a tendency to become coalesced and adherent to the skin through repeated exacerbations in periaadenitis, even though but one supraclavicular group be manifestly affected. It is the latter type which is so prone to early mediastinal invasion and to general hematogenous dissemina-

* Boston M. & S. J., 1914, CLXX, 123.

† J. Am. M. Ass., 1913, LXI, 2122.

tion with intraperitoneal involvement. Mediastinal infection is almost, and intraperitoneal extension is certainly, of hopeless prognosis and must so remain until more efficacious methods of treatment are developed.

The following treatment which has been and still is being developed is based upon this philosophy: fostering localization of the infection with earliest possible elimination of the same. The therapeutic procedures are regarded as primary and supplementary and have been applied as will be indicated to favorable and unfavorable cases.

Primary Procedures.—Portals of entry in so great a majority of individuals are to be found in the mouth, throat, nose and ear, that routine radical tonsillectomy, competent investigation and treatment of teeth, accessory nasal sinuses and ears are prerequisites and should often include skiagraphy.

The demonstration by Dr. Bunting of lesions of Hodgkin's disease, of the unmistakable Dorothy Reed type, in tonsils manifesting little, if any, abnormality, *in situ*, has confirmed the propriety of this attitude. In addition the likelihood of dissemination from these foci through the circulation, especially the lymphatic, is notoriously great. Organisms resembling *B. Hodgkini* morphologically have been observed in abscesses about the roots of teeth and in the discharges from nasal sinuses. The danger of gastrointestinal and even peribronchial infection from such sources is real if slight. Any real danger in this disease, be it however slight, is a grave danger and neglected may determine a fatal issue otherwise avoidable.

Surgical removal of the greatest portion of the disease that can be accomplished with safety, gentleness and thoroughness as advocated by Halsted in extirpating cancer, appears to do most to throw the balance of power in favor of the individual. This is always to be done after recovery from tonsillectomy which is best accomplished, when possible, under local anesthesia. Virtually as complete an excision as that advocated by Crile in cancer of the cervical glands should be made, for involvement is always wider than appears externally and has often extended to all the regionary glands. When excision is incomplete, recurrences are generally prompt and these early recurrences usually manifest decidedly increased virulence. Since the microorganisms are probably present in the periglandular tissue, it is impossible to overestimate the importance of thoroughness, gentleness and the sharpest possible dissection and of not operating during a period of acute peradenitis. It is, moreover, inconceivable under any condition that the field of operation could remain uncontaminated. This, therefore, should be thoroughly treated with tincture of iodine and drained. The immediate reaction is greater and the healing not so smooth but the tendency to recurrence is definitely reduced. Incidentally scar tissue is notoriously poor soil for the persistence of infection. A patient's resistance is not long or materially reduced by this type of intervention and there is a deal of comfort in the realization that many bacteria and their toxins, together with degenerate tissue the result thereof, are truly innocuous *in vitro*.

One emaciated child of five succumbed to an ill-advised operation. One woman died from an anesthetic before an operation to decompress her mediastinum could be begun.

With these exceptions, not even many repeated interventions on the same individual have been followed by more than temporary distress, and not to our knowledge has the course of the disease been unfavorably affected by surgical work when done according to the principles enumerated above. On the other hand excisions and re-excisions are commonly followed by improvement other methods have failed to achieve.

Supplementary Procedures.—The whole area of operation should be subjected to X-rays, in measured doses, begun the same or the first or second day after excision and repeated thereafter as frequently and for as long a time as safety permits. Wherever else the disease is present or suspected, should be also thoroughly treated. Dr. Foerster and Dr. Baer have spared neither time nor pains in cooperating in this work and it is quite impossible to estimate how greatly these patients, nearly all of them indigent, have benefited by their generous attention.

Control observations from the same individual indicate that it is impossible to obtain cultures from glands after they have been thoroughly X-rayed, that such glands and periglandular tissue show increased sclerosis with the appearance of more giant cells and hyaline degeneration within the glands. Moreover, individual glands, and those in chains and groups, that have been shown histologically to have been the seat of definite Hodgkin's disease have disappeared more or less completely and remained stationary for two, three and five years after X-ray treatment given subsequent to the removal of exciting foci. No such result is unfortunately as yet to be recorded in retrosternal involvement.

Vaccine.—Our experience is too limited to make possible any statement as to curative results from this treatment. Each case receiving vaccine treatment is being followed with repeated blood studies by Dr. Bunting, who is kept in ignorance of the source of the specimen and the nature of the treatment. Unquestionably there may be temporary subjective and apparently objective improvement attributable to the vaccine. Certainly there may be actual harm done even with small doses. We believe that until more is known of the late and permanent results of vaccination it is essential to regard this as a part of a method of treatment, be it curative or prophylactic against recurrence, which is as yet of insufficiently demonstrated value.

Serum.—A startling similarity, noted by Bunting in the lesions of the experimental disease in monkeys, in very acute human disease and in those occurring in fatal diphtheria, together with the diphtheroid type of organism, suggested a possibility of benefit to be obtained from administration of diphtheria antitoxin. This has been given adequate trial. Some subjective and possibly some objective improvement followed its use. This questionable improvement was transient at best and nothing to warrant its routine administration was noted. The serum was assumed to be without any specific action.

Comparison of three varieties of antitoxic serum and one normal horse serum as to bacterial agglutinins and lysins for different strains of *B. Hodgkini* and *B. diphtheria* disclosed no regularity in action.

Transfusion has not been found to be of any lasting value, not even in the presence of spontaneous hemorrhages as it was impossible after repeated transfusions, to restore the platelets to the circulation.

Drugs.—Persistence of the arsenical superstition, together with a temporary suspicion that the disease was due to a fungus, led to the administration of salvarsan intra-muscularly and intravenously. In febrile cases it may reduce the temperature to normal for a day or two, and even cause splenic and hepatic enlargements to diminish materially but only temporarily. It was without appreciable effect upon the ultimate outcome. Tonics are often of a great service, but arsenic no more than iron. Benzol has not been given.

Hygiene.—Too much importance cannot be attached to maintaining these individuals upon the highest possible level of general physiological efficiency. Recurrences are prone to appear upon the wake of any considerable or even slight phase of deficiency. Mental depression over a short period has seemed sufficient to induce a recrudescence.

Recurrences.—Glands have been repeatedly excised from regions (necks and axillæ), previously operated upon, which have finally remained free from any evidence of disease, some for upwards of three years. In one individual, with a late return (four years), glands excised showed but an ordinary chronic adenitis, indicating strongly the probability of local cure, after two previous operations when tissue excised was histologically that of Hodgkin's disease. Another patient upon three occasions became slightly febrile with recurrences of only an axillary gland or two in each instance, but the temperature returned to normal promptly after their excision. Moreover, later recurrences manifest a tendency, if the histological picture be a criterion, to exhibit an increasing chronicity in the process.

It is impossible to forecast what any recurrent gland will do under otherwise favorable conditions and under any form of treatment save that even a small one may act as a primary focus in the dissemination of both toxin and infection. It is best, therefore, to excise the gland under local anesthesia, which can be done safely and with trifling distress. The surest remedy is self-evident—a course of X-ray exposures is again to be instituted as if it were a primary operation. It is probable that this treatment should be repeated periodically as a prophylactic against recurrence.

Unfavorable Cases.—We are attempting to institute such supplementary procedures as eventually may make the application of more definitely curative primary procedures possible and justifiable.

That progress in dissemination which typifies Hodgkin's disease may be likened to a row of children's blocks. If the first be upset unless the sequence be broken the whole series will fall. Unfortunately, in this disease, merely breaking the sequence may avail little as any hiatus is more than likely to be crossed, if in addition, the upsetting force be uncontrolled. Probably no part of the chain is more vicious than the initial lesion which should therefore be eliminated if conditions permit. Usually this is demanded if anything is to be attempted in the line of curative therapy.

Any or all methods of combined treatment frequently retard the progress of the disease, indeed may even induce a protracted regression with a prolongation of a relatively comfortable and hopeful existence.

This much is at present attainable and optimism indicates the future possibility of some recoveries even under these adverse conditions, as a stimulating encouragement—at least one may find comfort in the knowledge that the mortality rate cannot be increased.

Results.—Early Hodgkin's disease, at least that form exhibiting the changes described by Reed, is curable if spontaneous recovery seldom or never occurs.

A cure or recovery we consider as established only when an individual shows no trace of the disease, and has a normal blood picture, four to five years after manifest glandular enlargement has disappeared. This extreme position is justified by the knowledge that recrudescence can occur after a shorter period of apparent freedom from disease. Upon this basis, we have but six cases to report:

CASE I.—June, 1908. R. B., female, æt. 32. Duration over a year. Seen two days before death. Very extensive involvement; most intense distress which was uncontrollable by opium. Death due to anesthetic given in an attempt to decompress mediastinum which was filled with a mass of glands almost as large as the heart itself.

CASE II.—October 8, 1908. W. R., male, æt. 10. Duration one year. Left side of neck from mastoid to below level of clavicle and from midline in front to behind anterior margin of trapezius occupied by mass of glands, not coalesced, not adherent to skin.

October 10, 1908. Complete excision. Positive Hodgkin's disease histologically. Cultures negative. Prompt recovery. Smooth healing. X-ray treatment begun and continued.

June 24, 1909. Began to look and feel badly. Recurrence in region of submaxillary gland. Has not been rayed recently.

August 15, 1909. Recurrence. Excision. Histologically Hodgkin's disease. Recovery smooth. X-ray started again.

October 22, 1910. General condition excellent. Slightly enlarged glands at tip of hyoid process and at outer margin of base of mastoid. Chest and abdomen negative.

July 1, 1913. Two more glands present in region of submaxillary. Those noted above, present and unchanged. All excised. All negative histologically.

January 27, 1914. Apparently well on critical physical examination. Blood count indicated recurrence which was disclosed by stereoscopic X-ray (Eisen) in a gland lying behind the left sternoclavicular articulation.

March 9, 1914. General condition excellent. Has been getting polyvalent sensitized vaccine (Rosenow). Gland increasing in size.

CASE III.—October 9, 1908. W. B., male, æt. 33. Duration six months. Itching of skin was first symptom. Dense fist-sized mass in left supraclavicular region. Overlying skin boggy. Smaller mass in apex of left axilla. Dullness over upper mediastinum. Treatment refused. Took several courses of X-ray treatment with little effect. Mud baths were curiously without beneficial result.

April 20, 1909. Death. No necropsy.

CASE IV.—October 30, 1908. K. F. B., male, æt. 22. Nasopharyngeal irritation six months before. Felt off color. Recently noted few enlarged bilateral cervical and axillary glands. Mainly in posterior triangles. Groins, abdomen and chest negative.

November, 1908. Glands excised for diagnosis. Positive Hodgkin's disease. Tonsillectomy followed by X-ray treatment. Hygienic measures.

December, 1912. Few glands smaller than peas in left posterior triangle, one gland smaller than pea in right posterior triangle. Axillæ similar. Groins and abdomen negative.

January, 1914. Reported to Dr. Bunting. Health excellent. Blood picture normal. It was from the study of this blood previously that the characteristic blood changes were recognized.

CASE V.—September, 1909. G. R., male, æt. 8. Enlarged glands noted by public school nurse eight months before. No effect on general health. History unimportant. Large mass of glands below angle of left jaw. No general glandular enlargement. Chest and abdomen negative.

September 30, 1909. Gland removed for diagnosis. Positive.

November 15, 1909. Cervical mass excised. Marked periglandular sclerosis. Incomplete operation. Tonsillectomy. X-ray and hygienic treatment.

September 7, 1910. Recurrence noted beneath angle of jaw. Excised. Positive Hodgkin's disease.

October 8, 1910. von Pirquet test negative.

November 25, 1910. General condition excellent. No recurrence. Mediastinum free.

February 9, 1911. General condition good. Small glands in both sides of neck and both axillæ.

March 7, 1911. Readmitted to hospital because of profuse nose-bleeds. Coagulation time six to seven minutes. Subsided under rest and administration of horse serum (?).

April 20, 1911. Again admitted to hospital. Bleeding from nose and gums. Anæmic. Febrile. Spleen enlarged. Abdomen distended. Transfused—mother.

May 1, 1911. Again transfused—mother.

May 9, 1911. Again transfused—brother.

May 17, 1911. Onset of first marked attack of continued fever.

May 22, 1911. 0.3 gm. "606" in buttocks. Some effect on temperature.

June 15, 1911. Recurrence of febrile state. Given 0.3 gm. "606" intravenously. Reduction of temperature but for two days only. Decrease noted in size of spleen and liver which had lately become enlarged.

July 22, 1911. Another attack of Pel-Ebstein fever with epistaxis. Liver smaller, spleen same size.

August 21, 1911. Recurrence of fever. Spleen large, liver smaller.

September 1, 1911. Only evidence of disease in glands in group about submaxillary. Excised. Positive Hodgkin's disease. Emulsified and injected into guinea pigs. No effect. Cultures: White coccus and *B. subtilis*.

September 20, 1911. First recurrence of fever since operation. Bleeding from nose and gums.

October 16, 1911. Fever continued. Rapid local recurrence of gland under ear. 0.2 gm. "606" intravenously without effect.

January 23, 1912. Gradually failed. Increasing emaciation and abdominal distension. Death from starvation. Necropsy—chylous ascites. Advanced retroperitoneal lymph gland involvement. General wasting. Anæmia. Cultures—contaminated.

CASE VI.—December 2, 1909. F. v. S., male, æt. 10. Under nourished. Slightly enlarged glands both sides of neck, both axillæ and both groins. Abdomen negative. Harsh and prolonged expiration at left apex. Blood positive Hodgkin's disease.

January 10, 1910. Tonsillectomy. Glands for diagnosis from groin, neck and axillæ. Cervical glands positive Hodgkin's disease. X-ray and hygienic treatment.

April 26, 1910. Slight glandular enlargement persists. Growing rapidly and gaining in weight.

October 5, 1910. Still gaining. von Pirquet test positive. Glands remain the same.

September 10, 1913. Glandular condition about same. Harsh breathing at left upper. von Pirquet test positive. Few slightly enlarged glands palpable.

January 6, 1914. General condition excellent. Blood picture normal. Glands quiescent.

Obviously so small a number of cases is of little value, save in the lessons to be learned from mistakes.

Case I was virtually dying. Intervention was prompted only by desire to relieve a degree of distress too great to admit of description. Treated early in the disease, the outlook would have been excellent.

Case III, almost certainly hopelessly involved when first seen, possibly illustrates the impotence of the X-ray to control the progress of the disease so long as the primary focus and the major portion of the disease remains. Prognosis was probably bad from the outset because of early extension of the disease to the mediastinum.

Case V illustrates the harmful results of incomplete surgical intervention. This boy was of the puny type and a congenital pessimist. Had better judgment prevailed and the slightly added risk of a complete radical excision been accepted primarily, it is conceivable that this life might have been saved.

Case II, apparently more unfavorable than Case V primarily, was treated the more radically because of supposed hopelessness otherwise. This child was discouragingly puny, but an aggressive optimist. First recurrence (9 months) accompanied evident deterioration in general health with prompt improvement following excision. Suspected recurrence three years after the first was unaccompanied by any effect upon general health. Microscopic examination proved these glands to be free of changes due to Hodgkin's disease. Finally four and one-half years after last positive evidence of the disease was found, while feeling perfectly well and after repeated physical examinations with special attention directed to the mediastinum had failed to disclose any evidence of disease, a routine blood examination indicated a recrudescence. Stereoscopic skiagrams revealed glandular enlargement behind the left sterno-clavicular articulation. The primary operation had extended down to the region of the thoracic duct, indeed it was probably injured and ligated.

Cases IV and VI, both nephews of physicians were given every benefit of early and late treatment and serve as proof that the disease is curable without the aid of any specific therapy.

In conclusion even these few cases indicate that primarily Hodgkin's disease is a localized process, susceptible of cure when properly treated as a malign, though chronic infection. It may persist for years without manifesting itself save in the blood picture so that cures may not be assumed until after an uninterrupted duration of years of persistently normal conditions.

A sovereign remedy for all cases is not now conceivable. At present the greatest need is some therapeutic agency to control glands not directly accessible; for once extension, which may occur early, has reached either the thorax or abdomen the prognosis becomes relatively, if not absolutely hopeless.

SOME UNPUBLISHED WATER-COLOR SKETCHES OF SIR CHARLES BELL,* WITH OBSERVATIONS ON HIS ARTISTIC QUALITIES.†

By EUGENE R. CORSON, M. D., Savannah, Ga.

I bring these unpublished sketches of Sir Charles Bell before the profession, first, with the hope, that it may induce others better situated than myself to publish other sketches of his, both drawings and paintings, stowed away in England in museums, and out of the way places, perhaps, whose publication at this time, when photography is so universal and the free hand of the true artist so rare, should stimulate us to more artistic work in anatomy and medicine generally. And, secondly, because I believe a study of Sir Charles's artistic work will attract us to the relationship of Art to Medicine, give an added impulse to the study of artistic anatomy, and show wherein we may improve our methods in the mere study of anatomy itself.

To call these sketches, which I have the honor and the pleasure to present to you, "unpublished" demands some qualification. They have never been reproduced as such, but they were provisional sketches to serve as "copy" for his etchings in his work on the arteries, the first edition of which appeared in 1801. But the very fact that they did serve as provisional sketches makes them, in my mind, of greater value, for they show Sir Charles's methods of work, and exemplify certain principles in anatomical delineation well worthy of our consideration.

In a letter to his brother George, written on January 8, 1805, he wrote:

I am doing my sketches in water-colours complete, out and out, leaving it for after-determination how they may be engraved.

The majority of the sketches were done about or before 1800 and these words apply equally well to them. With the

* These sketches were bequeathed by the late Dr. Thomas Windsor, of Manchester (see British Medical Journal, London, June 11, 1910), to the Library of the Surgeon General's Office, Washington, D. C., and he was undoubtedly influenced to make this bequest through his friendship for the late Dr. John S. Billings, at one time its librarian.

The twelve plates are most of them 10½ by 8 inches in size, in water-color, showing the high coloring and free brush work of a preliminary sketch, striking specimens of free-hand drawing direct from the dissection. They were drawn undoubtedly before or about the year 1800, when Sir Charles was still in Edinburgh working with his elder brother John, for with the accompanying explanatory script of the plates they form the "copy" for the first edition of his "Engravings of the Arteries," published in 1801.

Changes and additions were made in subsequent editions, especially in the third, which bears the date 1811, when the negro's head and the two plates designated as drawn by C. Cheney, were introduced. As frequently happens, the pupil, drawing under the eye of the master, copies him, while the master's own touches make the picture more the master's than the pupil's. Sir Charles, to compliment a favorite pupil, designates him as the artist. So I interpret it.

† Paper presented at the XVIIth International Congress of Medicine, London, August 6-12, 1913. Section XXIII, History of Medicine.

instinct of the true artist he must try out by sketch before attempting the finished picture; and comparing the two before us, we see how he worked and wherein the finished picture excelled or missed the excellence of the first sketch. Sir Charles has himself well contrasted the sketch with the finished picture in his "Anatomy of Expression," when treating of the uses of anatomy to the painter. He writes:

It is true that the sketch is too often a mere indication of the painter's design, intended to be worked up to the truth of representation as he transfers it to the canvas—that the outlines of the figures are rather shadowy forms, undefined in their minute parts, than studies of anatomical expression, or as guides in the subsequent labour. And, perhaps, it is for this reason that there have been many painters, whose sketches all admire, but whose finished paintings fall short of public expectation. But a sketch that is without vigor, and in which the anatomy has not been defined, is a bad foundation for a good picture; and even a little exaggeration in this respect is not only agreeable, but highly useful. The anatomy should be strongly marked in the original design; and from the dead coloring to the finishing, its harshness and ruggedness should be gradually softened into the modesty of nature. The character of the sketch is spirit and life; the finished painting must combine smoothness and accuracy. That which was a harsh outline in the sketch or the strong marking of a swelling muscle, or the crossing of a vein will be indicated in the finished composition, perhaps, only by a tinge of color. The anatomy of the finished picture will always be most successful, and even most delicate, when the painter has a clear conception of the course and swelling of each muscle and vein which enters into the delineation of the action.*

Of these twelve water-colors the plates marked II and IX are supposedly by Charles Cheney; Plate II, the plan of the aortic system, might well be left to a favorite pupil or assistant. Figure 2 on Plate IX, representing a hand with the index finger resting on a book, which figures in the third edition of the engravings is designated as drawn by C. Cheney and etched by Charles Bell. The etching is somewhat larger than the sketch, and a decided improvement over it. Like Figure 3 in Plate VIII it is a much later sketch, and done on a free space on the paper used years before.

Plates XI and XII, which appeared in the first and second editions, were replaced by four much better illustrations in the third edition.

Plate VIII, which consists of three figures, appears in the third edition as a plate of one figure. In the first and second editions Figures 1 and 2 appear without Figure 3, while in the third edition both Figures 1 and 2 are withdrawn, and the dissected arm, of which Figure 3 forms the proximal end, is alone given. I should therefore say that probably Figure 3 was painted much later than the other figures and that the etching was made direct from the dissection. In other words,

*"The Anatomy and Philosophy of Expression as Connected with the Fine Arts," by Sir Charles Bell, K. H., 6th Edition, London, 1872, p. 227.

Figures 1 and 2 were drawn from dissections done in the early Edinburgh days, while Figure 3 is later London work, and indicates that he considered the dissection better adapted for his etching. It all shows his careful selection.

In Plate V, Figure 2 is reproduced, while Figure 1, which appears in the first and second editions, is replaced by another drawing to show the arteries of the face.

With these changes, the drawings have been reproduced by engraving or etching, and done by himself, with the exception of Plates II, III and X, which were etched by J. Stewart.

The accompanying script which is his own handwriting, in my judgment, is the script of a copy-book, written with great care and deliberation, when time seemed no object, but only the wish to produce an accurate and beautiful "copy" for the printer. It is like the delicate, precise handwriting of the Latin races. Throughout his life his handwriting changed but little; even when it shows rapidity, it is a beautiful flowing script, quite Spencerian in its curves and hair lines.

Examination of these sketches with a magnifier shows rapid work, with much of the drawing done with the brush itself. I see no pencil marks showing any drawing before taking up the brush. Even the coursing of the vessels is largely, if not wholly, rapid brush work, especially the smaller ramifications. The general outline of a head will be drawn with the brush, rapidly, and with a bold and free sweep. There is no hesitation anywhere, and he is sure of his drawing. He is not making any pictures, to be reproduced as such, but simply feeling his way to the more careful and accurate etching; and I cannot but believe, too, that the etching itself is made with the dissected part before him. John Bell ever insisted upon a careful copying of the dissection, and he taught this lesson to his younger brother with his wonted insistence and emphasis, and that Sir Charles learned his lesson well we have good evidence. Alluding to these very plates, he wrote: "I have etched most of the plates with my own hand, preferring accuracy to elegance."

While it was very evident from his published drawings how prolific his artistic work was, and how great his industry, these sketches give even better evidence of his rapidity and facility. In his first published work, *A System of Dissections*, there are many beautiful plates on a larger scale, which could have been easily reduced for the smaller work; but, no, his artistic sense and energy demanded new drawings and fresh dissections, and so we have a series of entirely different illustrations, additions, and improvements in the third edition which make it almost a new work. This in itself shows the artist and the man of science.

A comparison of the sketches with the etchings show some interesting and suggestive differences. Generally speaking, it may be said that as illustrations of dissections there is deterioration in the etchings. In the first place, five of the plates are much reduced in size. Size is an important factor in artistic conception, and in the grasp of the architectonic plan of any structure. Reduce Michael Angelo's David or the Venus of Milo to a one-foot figure, and no matter how

perfect the reduction, how much is lost! Great as the drawings of Vesalius are as faithful copies from nature, and especially so when compared with the work of his predecessors, much of the effectiveness of the faithful copy is lost in the small size. Even his imitators, who simply enlarged these drawings, took a great step forward. We turn the pages of the *De Humanis Corporis Fabrica* more quickly than the pages of the *Tabulae* of Albinus. Compare Sir Charles's small etchings of the arteries with Maclise's life-size drawings in Quain's splendid work. The etchings are more finished and delicate, but much less effective than the drawings of the less gifted artist, and almost entirely on account of the size. Of course the two works had different objects in view.

The trend of anatomical illustration is towards larger figures. Where the etching is the same size as the original sketch we can see the improvement from more careful drawing, and the greater distinctness of black and sharp lines. He was undoubtedly influenced in the small size of the other sketches by the subsequent etching. In the reproduction of Plate V Sir Charles himself, still influenced by the size of the prospective volume, has committed the error, rare with him, of overlooking the value of relationships in anatomical delineation, for in etching the arteries of the face, he has omitted the great trunk in the neck, well shown in the original sketch, and has etched for us a head cut off close to the base of the skull. A lack of proper relationships is worse than poor drawing. Sir Charles, of course, takes no liberties with his "copy"; he is always the faithful copyist. But J. Stewart, who etched Plate III, instead of faithfully copying the right iliac crest, as drawn for him, has seen fit, while Sir Charles's back was turned, to take every liberty with it, and he has given us a strangely scalloped bone. He also omitted the os pubis and ischium, which are in the original, and which give us the relationships of the iliac and beginning femoral arteries. He has, however, introduced the skull, omitted in the sketch, which shows he had the anatomical preparation before him.

While in a few instances the etched artery is better defined than the vessel drawn with the brush, it usually suffers in comparison, for the painted vessel is well accentuated, and even exaggerated. Exaggeration, when properly applied—for only the real artist can use it correctly—is a true principle of art. The Greeks had the audacity to increase the facial angle, and with what marvelous effect! The genius of Michael Angelo put its own limits on bony prominences and swelling muscles, and his drawings and plastic art are good anatomical models to-day.

The sketches, as well as the etchings, show an ever present sense of the third dimension. His drawings are never flat. Even in his descriptions of the ligations of the arteries, he is ever mindful of their depth. On this point examine Plate II (Third Edition), showing the femoral with its profunda branches; the drawing is almost stereoscopic. Many beautiful examples could be given to show this quality.

In a general way, it can be seen that Sir Charles has followed the principle which he sets forth in the essay from

which I have quoted, namely, that the anatomy should be strongly marked in the sketch, and in the finished picture "should be gradually softened into the modesty of nature." While this was probably the prevailing idea one hundred years ago, I am sure the best artists of to-day would modify it. Sir Charles strikes the real key-note of all anatomical delineation when he writes: "The character of the sketch is spirit and life." Art is the expression of life, and the more true and intense this expression, the more artistic. If the artist paints the dead body, it must suggest the life which has flown. If he paints the dissected body, the more clearly he shows us the parts in their true relationships with their relative values, *the more does he suggest their function*, and the more artistic does his work become. The conception cannot be too comprehensive, or too general; never yet has its deepest depths been sounded, and never yet has its surface been ever so lightly touched without some artistic response. Sir Charles, of course, is writing of art in general, and this principle is in a way more applicable there than in anatomical delineation proper. But in all his writings and in his most pretentious drawings, his aim ever was to raise anatomical and clinical drawings to a higher artistic level. He writes in one of his letters to his brother George: "Sometimes I think of finishing my anatomy of the muscles in painting in great style." This was a great idea and we should endeavor to carry it out to its fullest extent; and if our science of anatomy is to grow into greater proportions and more intimate knowledge of growth, development, and *function*, its artistic expression must grow with it.

I well remember when a young medical student looking with longing eye at a fine copy, beautifully bound, of Sir Charles Bell's "System of Dissections" displayed in a shop window and opened at one of the most attractive plates, and having to content myself with the two-volume edition of his "Surgery" which I got for a song. And now after many years, I find myself looking at these same plates with even a greater pleasure, and an added appreciation. What is the charm? In what does the excellence consist?

We all know that with every true artist some bit of the personality flows out at the end of the pencil, which eludes us and cannot be expressed in words; but there are canons of excellence in Art, which can be expressed, and which we can apply in our estimation of an artistic work, even when it comes to the drawing of the dissected parts of a dead body. Some subjects so lend themselves to the artist's touch that a certain perfection may be attained by talent not of the first order, but when the subject lies outside the usual field, in fact, seems the farthest removed from any artistic treatment, it requires a higher order of talent or genius itself to bring it within the confines of Art. And it is wonderful how genius can do this for us. The real secret is, that it brings the dead to life; that in the dead body, it suggests or makes us see the life which has flown; that in the dissected arm, with the muscles and blood vessels bared, we see these muscles alive and functioning. This is the magic of Art; this is the great deception. The mere faithful copyist cannot do this.

The artistic talent of Sir Charles expressed itself in many ways. He used the pencil and the brush, he modeled in wax and plaster, and etched and engraved. He wished through the wax to catch and hold the colors of fresh pathological specimens, and to-day we are striving to do this very thing. I have not seen any of this work; there must be specimens of it somewhere in England.

According to a note in the "Letters," his sketches of the wounded at Waterloo he afterwards reproduced in water-colors, excelling in force and effect any professional paintings hitherto attempted. Many of them, together with some in oil, are now, along with those in the Windmill Street Museum, in the College of Surgeons, Edinburgh, and others in University College, London. Seventeen were presented by his widow, in 1867, to the Royal Hospital, Netley, along with his note book. In the Middlesex Hospital he made many drawings of cancer cases, but they seemed to him so distressing to look upon, he could not bear to publish them. This has always seemed strange to me.

It is interesting to note that his earliest published work, his "System of Dissections," was one of his most pretentious, and in many ways fully characterizes his qualities as an illustrator of anatomy. The drawings show a nice selection of the subject, the point of view from an artist's standpoint, the relationships of the parts with their relative values, and a skillful drawing of the different layers to show depth. There is no hesitation in the drawing; he seems always sure of the form; and whenever the subject admits it, you are aware of the feeling, a fine sentiment always, with touches of local color and surroundings to give a dramatic interest to the composition.

In Plate I, for example, in drawing the abdominal muscles, he has not only shown us the three layers, but the muscles which come into relationship with them, and he has so placed his subject that these muscles are made prominent and are seen to best advantage; and he has drawn for us the dead body itself. It lies stretched out before us with the extended arms, the set features, the relaxed jaw and staring eyes, well drawn and most striking; and yet there is nothing repulsive. The dead body itself has become of interest, and we ask involuntarily, "what manner of man was he?" It attracts and holds the attention. This is the dramatic element, which the true artist will always introduce, when possible. It has been discarded in modern anatomical drawing, and, I think, to its detriment.

In Plate VI he has drawn the open chest, with the heart and lungs in situ. Cutting through the costal cartilages he has turned back the sternum, showing the anterior mediastinal space better than I have seen it in any modern anatomy, and he brings out besides the courses of the internal mammary artery and the phrenic nerve in a way to impress them forever on the memory. The drawing is beautiful and striking; with the eye of the anatomist and the eye of the artist, he has chosen the true point of view, which the artist, by the way, is less apt to miss than the mere anatomist, no matter how well he can name the parts. I showed a drawing of the

shoulder girdle by John Flaxman to an anatomist recently, and he remarked "I never quite saw the clavicles before." It was all the point of view.

Plate XV, showing the femoral and its branches with the nerves on the anterior face of the thigh, is quite the perfection of anatomical drawing—certainly for showing the course of an artery and its deep branches—with the rest of the limb in outline, drawn with faint precision, without one unnecessary line. With consummate skill he shows us the relationship between the anterior crural nerve and the branches of the femoral, and the obturator nerve picked up by a tenaculum. When Sir Charles dissected this thigh, he not only made a skillful dissection, but he saw the true significance of the parts and gave them an artistic expression. This was his genius. To him the dead body was always alive and the impulse to draw it, whole or dissected, was as strong as the impulse to "frisk it" when he heard lively music. The drawing pencil was constantly in his hand and his drawings are legion; and I doubt not many a fine one worthy of reproduction lies hidden away somewhere in this great little island.

This work, begun in 1799, was completed in 1803, and at the same time he was making dissections and drawings for his three works on the anatomy of the brain, of the nerves, and of the arteries—work done well before he was thirty. Of his work on the arteries I have already spoken; of the plates on the nerves, we have good evidence of his skillful dissection and faithful copying from his subject, for he has drawn the courses of the nerves in delicate lines to their finer ramifications, with the flaccid and widely separated muscles consequent on nerve dissection.

With the modern anatomies before me, and the great advancement in the minute anatomy of the brain, I must confess to the charm and fascination of his plates. Though more than a century has passed, their delicate coloring still holds. But more than that, you see his comprehensive grasp of structure and how skillfully he brought it out. He reproduces but one plate from an outside source, one of the base of the brain, with the twelve cerebral nerves, from Vic d' Azyr, a bit of anatomy he was afterwards to work out so carefully and to draw for us in his own inimitable way.

And this prompts the observation how wholly his own his illustrations are, and entirely uninfluenced by outside sources. If he copies an old plate it is for its historical value. His treatment, his point of view, is his own always; and like his brother John, he never published a work which was not all himself.

When Sir Charles went to London in 1804, he carried with him the manuscript of his "Essays on the Anatomy of Expression," the illustrations for which were to show his ability to give expression to the emotions in portraiture. In the first edition, we find a number of little sketches, showing great facility in drawing as well as a keen sense of the delicate shades of facial expression; but quite aside from the merits of the illustrations, both the drawings and the text bring us face to face with the man. However excellent anatomical drawings may be, and individual too, in a way, they cannot

reflect the personality of the artist like a work dealing with the emotions and passions described as well as drawn. This work Sir Charles labored many years to perfect in the succeeding editions; he eliminated much that appeared in the first edition of 1806, and added more, and labored long to make his drawings what he wished them to be; and in doing all this, he laid bare his own nature with an unconscious abandon. In no other of his works, with the exception of his published letters, do we have revealed to us the man himself—his enthusiasm, his deep insight into structure and function, his general artistic sense and love of the beautiful, his sensibility to the moral and religious in life and art, and finally, a delicate and refined sentiment which pervades all his writings and all his drawings which can give an expression of this feeling. Mere intellectual brightness and smartness seem common enough, but real sentiment, in its best sense, is much less common. It draws a halo around the seeming commonplace; it gives an added push to enthusiasm; it gives a charm even to the drawings of the dissected body. With all our hard facts, let us cultivate sentiment and let us rejoice when we find it in a man of science. Only an artist of a fine and delicate sentiment would have drawn for us the face of the laughing child which closes the introduction to this work.

After Sir Charles went to London, though he carried on with equal assiduity his anatomical researches and his lectures on anatomy, his published drawings were chiefly to illustrate pathology and surgery and the incidents of the clinic. Many figure drawings of patients in the hospital are full of expression and sentiment, and you feel at once they are true to the life, and veritable portraits. He made many of these sketches at Portsmouth, after the battle of Corunna, and in Brussels, after the battle of Waterloo, and Baron Larrey, years later, recognized many of them on a visit to London. He conceived the idea of elaborate paintings and portraits, showing the patient and the disease. This seems to me a great idea. We may well take it up, for I see ahead the time when the advanced stages of malignant disease will be a rarity indeed, will pass away, in fact, and the medical historian will have to search past records to find the clinical features of inoperable cancer. They will be prized like the portraits of an extinct race. Many of his figure drawings, though mere outlines, showing malignant tumors, are of greatest value. His brother John had this gift of rapid sketching; but he was more inclined to complete the picture. One of his sketches, however, seems to me to surpass anything of Sir Charles's as evidence of deep feeling. It is his sketch of the case of Alexander Macdonald, evidently sarcoma of the arm.* Quite aside from its scientific value, he has made its pathos beautiful, a classic face of long suffering, and the disheveled hair almost like a wreath of laurel for the heroic fight of a brave spirit with death. The young man was dying when he made this sketch. He has brought a malignant tumor within the confines of Art, and no amount of mere skill in drawing can do this alone.

*The Principles of Surgery, by John Bell. London, 1808. Vol. 3, p. 82.



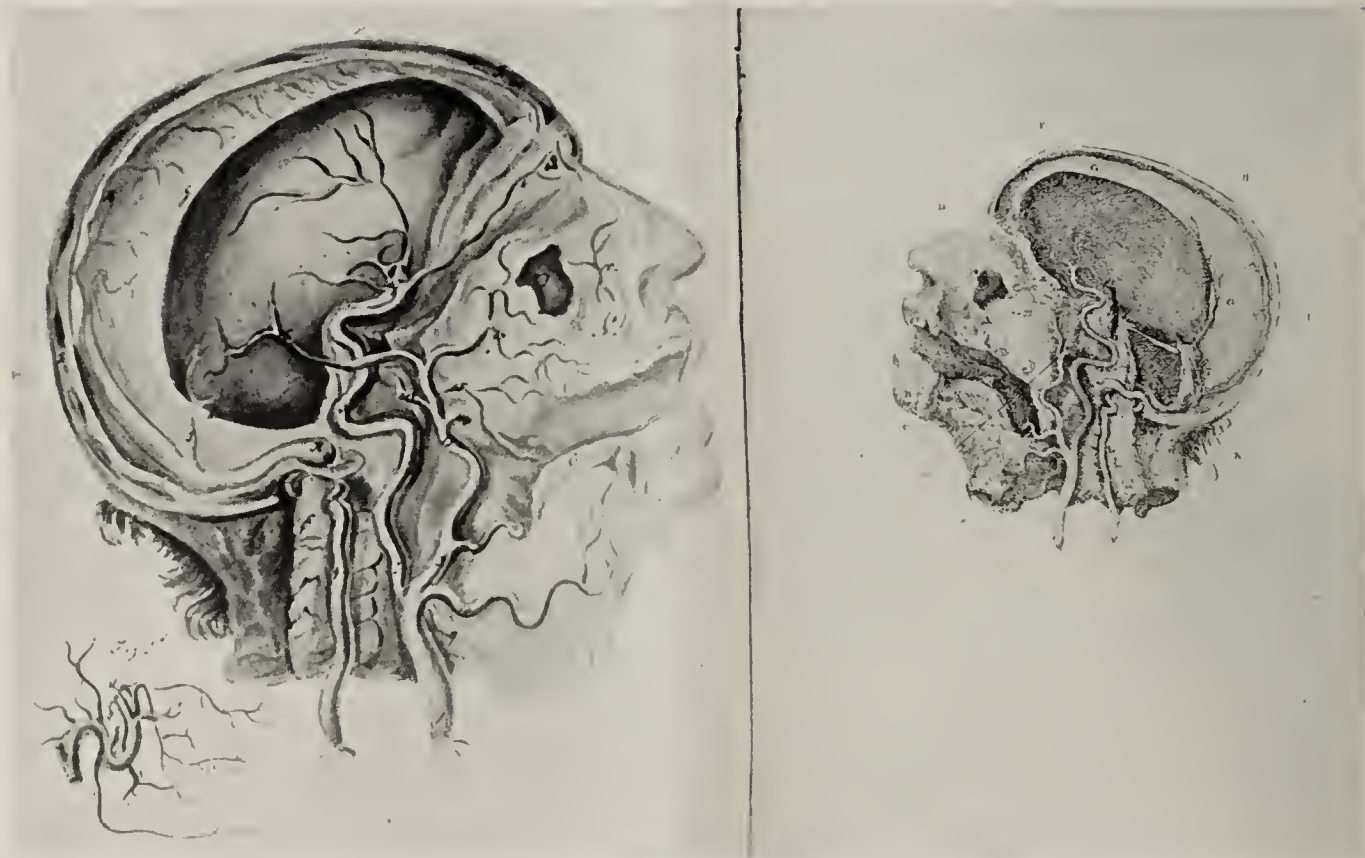
A



" PLATE IV."



" PLATE V."



" PLATE VI."

I cannot emphasize too strongly the value of these clinical sketches. Entering the hospital one morning he comes to a case of dislocation of the head of the femur and near by, one of fracture of its neck; and he draws for us most skillfully the clinical features; shortening, rigidity, and inversion of the foot in the one; eversion, shortening, and preternatural mobility in the other; we have nothing in modern illustration quite so good.

He conceived the idea of elaborate and artistic drawings of operations, and carried it out beautifully, drawing instruments in situ and the operative hand at work, or indicating the objective point of the operation. In his "Surgery" especially, are many of these little sketches in outline, always with an expressive hand holding an instrument, and showing at a glance what it would take a page to describe.

Though Sir Charles did so much for artistic delineation in anatomy and medicine, and wrote so much on the value of anatomy to the artist, it is only in passing reference and hints in his letters that he has anything to say of the application of Art to anatomy and medicine, to us at least, a much more important subject. He did think anatomy of great use to the artist, both in painting and statuary, and he has given us strong reasons for his belief. In this he went further than his brother John, who, while admitting its value, considered it rather limited and sharply defined; unless controlled by genius, the anatomy was apt to become too conscious a part in the conception and execution. But a great book is yet to be written on the value of Art to anatomy and medicine. Choulant * * * in his admirable work on the history of anatomical delineation down to 1850, has done much in an historical and bibliographical way to show the advances from ignorance and fancy to the true copying from nature; but the real application of the principles of Art to anatomy, and all it will mean in the future development of that science awaits its expounder. Certainly if we are to attract artists to anatomical studies, the anatomy itself should be treated from an artistic standpoint. We must bring Art to anatomy before we carry it to the artist; they can be made reciprocal. But the greatest influence of Art applied to anatomy will be in its teaching, and in making this teaching most effective. A study of mere form or structure without its life is the most barren of all

*Geschichte und Bibliographie der anatomischen Abbildung, nach ihrer Beziehung auf anatomische Wissenschaft und bildende Kunst, von Dr. Ludwig Choulant. Leipzig, 1852.

studies. He who sees the form without the life back of it, sees nothing; and the more we make the form give expression to its life, the more truly artistic it becomes.

The time must come when the dissecting room will offer not only the dead body for dissection, but will help show in every way, the life of its parts. Dissecting the muscles of an arm, the student will have by him the well developed arm of the athlete to show the muscles alive.*

Sir Charles, as I have said, conceived the idea of anatomical delineation on a grand scale, but only partially attempted to carry it out. If we can get an Abbey to paint for us the Holy Grail, let us have an equally great artist paint for us the dissected body, that we may best grasp its life. It would be a great stimulus to anatomical study. Only then will our anatomy become truly significant; only then shall we have a real artistic anatomy; and then what seemed commonplace will become interesting and even beautiful.

The genius of Sir Charles Bell was towards this end; it was his genius to discern the function back of the form, and with a confident and ready hand to draw for us what he saw. He had the artistic sense of proportion, of relationship, of relative values, of the point of view; and with it all that delicate and beautiful sentiment which colored his life as well as his art. It was indeed Goethe's *milde Macht* and the *Sweetness and Light* of Matthew Arnold.

A. John Bell's sketch of the case of Alexander Macdonald showing the artistic drawing of a malignant tumor, evidently sarcoma.

PLATE 4.—Drawing of a dissection of a negro's head, showing the external carotid and its branches. It shows the free brush work. In the etching we see the more careful working up of details and a better drawing of the artery. Reduced about one-third.

PLATE 5.—Drawing and etching showing the arteries of the face. The drawing is much superior. The etching seems to be made from a different sketch. Reduced about one-third.

PLATE 6.—Drawing and etching showing the internal and external carotid, and vertebral arteries. The drawing and etching show many differences; the drawing is much more effective. Reduced about one-third.

*Sir Charles had this very idea and carried it out in a way in his lectures. (See a paper by Dr. W. W. Keen in the Transactions of the 7th International Medical Congress, 1881, "On the Systematic Use of the Living Model as a Means of Illustration in Teaching Anatomy.") The best modern work which has come to my notice, which treats of artistic anatomy with a living model, is Kollmann's "Plastische Anatomie des menschlichen Körpers für Künstler und Freunde der Kunst, von Dr. Julius Kollmann. Leipzig, 1910.

JOHNS HOPKINS HOSPITAL BULLETIN.

The Hospital Bulletin contains details of hospital and dispensary practice; abstracts of papers read and other proceedings of the Medical Society of the Hospital, reports of lectures, and other matters of general interest in connection with the work of the Hospital. It is issued monthly. Volume XXV is now in progress. The subscription price is \$2.00 per year.

(Foreign postage, 50 cents.) Price of cloth-bound volumes, \$2.50 each.

A complete index to Vol. I-XVI of the Bulletin has been issued. Price 50 cents, bound in cloth.

NOTES ON NEW BOOKS.

Social Work in Hospitals: A Contribution to Progressive Medicine. By IDA M. CANNON, R. N. \$1.50. (Survey Associates, Inc., Publishers for the Russel Sage Foundation.)

There is no one so well qualified as Miss Cannon to interpret the uses of hospital social service, not only by reason of the study she has made of the subject, but because she has put so much of herself into the movement and has been so live an influence in its development.

Miss Cannon's is the first text-book on social work in hospitals that has been published, and though she feels that notwithstanding the widespread interest in the movement it is of too recent date and the experience gained of too experimental a nature to justify the laying down of dogmatic rules, either as to the function of the social worker or the proper organization of the work; still she points to certain ideals that have developed and fundamental principles that have been evolved.

She follows the history of hospital social service from the beginnings, referring to the social work of the medical students at The Johns Hopkins Hospital, under Dr. C. P. Emmerson, as one of the four important contributions towards the development of the movement, through its various phases and problems to the future ideals and possibilities. The book is full of helpful suggestions, dwelling upon the importance of thorough social training and efficiency and pointing out the dangers and pitfalls consequent upon poor standards. She puts before us, in a convincing manner, the interdependence of medical and social diagnosis and treatment.

Miss Cannon's book is a constructive piece of work that should be read by those interested in hospital management as well as by physicians, nurses and social workers.

Lectures on Tuberculosis to Nurses. OLLIVER BRUCE, M. R. C. S., L. R. C. P. \$1. (New York: Paul B. Hoeber, 1913.)

This book is "based on a course of lectures" delivered to the Queen Victoria Jubilee Nurses. The value to nurses of a description in detail of opsonic index technic, also of methods of physical examination of patients is questionable. The opsonic index is mentioned too often throughout the work, considering the present views of any value it may have in tuberculosis work.

Such a course of lectures would be of benefit to a junior medical student, but can hardly be useful as a standard for nurses.

Diseases of the Digestive Canal. By DR. PAUL COHNHEIM. Edited and translated by DUDLEY FULTON, M. D. Illustrated. Third edition. \$4. (Philadelphia and London: J. B. Lippincott Company, 1914.)

That the profession have recognized the value of Cohnheim's work is indicated by the fact that the publishers have brought out a new edition, which varies but slightly from its predecessor. It is a well written, helpful book for students and general practitioners.

The American Illustrated Medical Dictionary. By W. A. NEWMAN DORLAND, M. D. Seventh edition. Revised and enlarged. \$4.50. (Philadelphia and London: W. B. Saunders Company, 1913.)

The author has added five thousand terms to his previous edition, and his work continues to grow in value, and with each new issue its popularity will become greater. With the active growth in medical and allied sciences such a dictionary becomes absolutely essential to all students, and Dr. Dorland's can be recommended most heartily.

The Surgical Clinics of John B. Murphy, M. D. (December, 1913.) Published Bi-Monthly. (Philadelphia and London: W. B. Saunders Company.)

The majority of the papers in this number deal with bone lesions, and are well illustrated by X-ray photographs. Those anxious to learn how Dr. Murphy conducts a students' clinic will secure a good impression of his manner and style by reading the concluding paper in this issue of the "Clinics."

Oxford Medical Publications: Manual of Surgery. By ALEXIS THOMSON and ALEXANDER MILES. Vol. III. Operative Surgery. Second edition. Illustrated. \$3.50. (London: Henry Frowde and Hodder & Stoughton, 1913.)

This Edinburgh surgery is one that must appeal to many students and operators. The text is concise, simple, and practical, and the illustrations clear and well chosen. The authors are acquainted fully with the work done in foreign clinics, and their manual is, to put it simply, excellent.

A Text-Book of Physiology for Medical Students and Physicians. By WILLIAM H. HOWELL, M. D., etc. Fifth edition. Thoroughly revised. \$4. (Philadelphia and London: W. B. Saunders Company, 1913.)

No fresh word of commendation is needed for this famous classic. To every real student a new edition of this book is a true pleasure; and it is a source of infinite satisfaction to him to have Dr. Howell's views on the latest work along physiological lines.

Practitioners' Visiting List. \$1.25. (Philadelphia and New York: Lea & Febiger, 1914.)

The publishers have issued an attractive book, well suited to the needs of many practitioners. It is furnished with a large variety of tables to which reference is frequently useful. The "List" is practically arranged, convenient, and neat in appearance.

Progressive Medicine. Edited by HOBART AMORY HARE, M. D. Assisted by LEIGHTON F. APPLEMAN, M. D. Vol. IV. December, 1913.

This volume contains reviews of diseases and surgical conditions of many of the abdominal organs, and of the surgery of the extremities and tumors, and of such problems as anæsthesia, shock and infections. The need of "Progressive Medicine" is distinct, and the publication is prepared with ability and thoroughness, so that it is of real value to the majority of the medical profession.

Pyorrhea Alveolaris. By FRIEDRICH HECKER, M. D. \$2. (St. Louis: C. V. Mosby Company, 1913.)

The author is a dentist as well as a physician, so that he has had ample opportunity to become acquainted with this disease, but it is to be feared that he is on the wrong track in attempting to distinguish eleven different varieties of this affection. Further study will probably show that this classification can be much simplified when the causative organism is finally distinguished. The pathological illustrations are marred by the lettering, and the book adds nothing to what is already known about this disease.

Chloride of Lime in Sanitation. By ALBERT H. HOOKER. (New York: John Wiley & Sons, 1913.)

This little book of some 200 pages contains an excellent historical account of the development of our knowledge of the chemistry of the chloride of lime of which calcium hypochlorite,

CaOCl_2 , is the active disinfecting agent, together with elaborate directions for its practical use. The extent to which this disinfectant is being employed is well illustrated by the rather voluminous literature cited. It should prove of great value to practical sanitarians.

Causes and Cures of Crime. By THOMAS SPEED MOSBY. (St. Louis: C. V. Mosby Company, 1913.)

Mr. Mosby is a lawyer and a former pardon attorney of the State of Missouri. He has seen many criminals, and read widely, judging from numerous extracts in this volume, on penology, but he has compiled a work quite elementary in character and one which offers no new suggestions to the real student of this subject. The photographs of criminals inserted here and there in the volume are not helpful to the reader, for there is no reference to them in the text.

London Medical Publications: The Principles and Practice of Medical Hydrology. By R. FORTESCUE FOX, M. D. (London). (London: University of London Press.)

Medical hydrology or hydrotherapy is a subject not so well understood, either by doctors or nurses, as it should be, and here is a book on this method of treatment which is distinctly helpful. It is not a profound treatise on hydrotherapy, but a clearly written guide book covering the essentials in a simple and satisfactory manner. It is divided into four parts: 1, The Physiology of Bathing; 2, Hydrotherapy; 3, Medicinal Springs and Baths; and 4, Indications for Hydrological Treatment.

The Diseases of Children. By HENRY ENOS TULEY, M. D. Second revised edition. (St. Louis: C. V. Mosby Company, 1913.)

This book now appears in its second edition and consists of 597 pages. Many chapters have been rewritten, and a few illustrations have been added. In the appendix, the Standards and Methods for the production of Certified Milk as adopted by The American Association of Medical Milk Commissions are given. These standards are chiefly of interest to the producer of milk and from the point of view of the reviewer add but little to the value of the book for students and practitioners. The present day tendency is toward simpler methods in the feeding of infants. The complicated formulæ for the modification of milk found in the appendix are not only of questionable value but are confusing to one desirous of obtaining practical information along this line. Their use should not be advised. The text is written with a disregard for the proper English construction of the sentences and in many instances authenticity for the statement of facts is lacking. By way of illustration, on page 275, the author says, "In no class of cases does a complete climatic change have so beneficial an action as in children convalescing from enterocolitis. From points south of Mason and Dixon's Line, no other change is more beneficial than removal to points in Michigan. The large amount of water through this state imparts a life-giving something to the air which works wonders in these cases." Many of the illustrations are poor and unnecessary. Some of them (pages 101, 102, 110) may be of interest to the agriculturalist and to the producer of milk, but scarcely to students of medicine. The book which is intended for the student and the general practitioner does not fulfill its purpose satisfactorily.

Treatment of Tuberculosis. By ALBERT ROBIN, M. D. Translated by LÉON BLANC, M. D. \$5.25. (New York: The Macmillan Company, 1913.)

This work of 600 pages is the first English edition translated from the French by Dr. Léon Blanc.

The author deals with the subject from two main standpoints: the soil and the germ, and emphasizes greatly the question of the

soil. His contention, "contagion is not all in all in tuberculosis," is made unnecessarily emphatic, as predisposition in general is a fact recognized by the profession.

It is claimed that great reliance should be placed on drug medication in treatment. This is not in accordance with the view generally held, and the author fails to prove his claim.

Tuberculin is given scant praise, and such a statement as "the greater the gravity of tuberculosis the weaker should be the initial dose," is mystifying, and even if true would require some explanation of proof.

Altogether the book is only fair. It is written for the general practitioner and some of the matter could be taken out without lessening the value of the work.

The translation is very good—the English being good and easily readable.

International Clinics. Vol. IV. 23d series. \$2. (Philadelphia and London: J. B. Lippincott Company, 1913.)

Medicine, surgery and neurology are well represented in the "Clinics." Some of these are too long, but the papers by Warthin, Sewall, and Proescher are among the best in the volume. Some of the more modern views in neurology are presented in one or two papers, and eugenics is abused by having two articles attributed to it, which would be better classified under some other heading. The term eugenics is generally misunderstood and misapplied by American writers.

Cunningham's Text-Book of Anatomy. Edited by ARTHUR ROBINSON, M. D., F. R. C. S., Ed. Fourth edition. Enlarged and rewritten. Illustrated. \$6.50. (New York: William Wood & Co., 1913.)

From the title one would naturally infer that this work was like Gray's, that is, the writing of one anatomist; on the contrary, it is the reverse, there being for this last edition eleven contributors, all Englishmen, and there is, what is more striking, no chapter by Cunningham. But as he was the originator of this compilation it still partly bears his name and is one of Gray's chief competitors in the medical schools, which is an honor in itself, since the anatomy by Gray is conceded to be unsurpassed in English as the work of a single author. Cunningham's Text-Book in its new form is undoubtedly a book that will appeal to students for it is very liberally illustrated, uses the B. N. A. nomenclature, has an admirable index, and the text has been carefully revised and is modern.

A Practical Treatise on Medical Diagnosis for Students and Physicians. By JOHN H. MUSSEY, M. D., etc. Sixth edition. Revised by JOHN H. MUSSEY, JR., M. D. Illustrated. (Philadelphia and New York: Lea & Febiger, 1913.)

So many additions of various sorts have been made to the methods of medical diagnosis since eight years ago when the last edition of Mussey appeared, that it was essential, if his excellent work were to continue useful, that it be brought up to date. This has been done by his son, who has found it necessary to revise largely his father's book by additions and eliminations; but in general scope and character this treatise retains its original character which all who knew the elder Mussey value for his sake.

A Manual of X-Ray Technic. By ARTHUR C. CHRISTIE, Medical Corps, U. S. A. Illustrated. \$2. (Philadelphia and London: J. B. Lippincott Company.)

The clear and concise descriptions throughout the book, especially those pertaining to the electro-mechanics of X-Ray, well merit popularity, and to the man who is just "starting" Roentgenology the work should be a help.

Aside from this the reader will gain little, as the methods of interpretation and diagnosis are too brief and hardly abreast of the times. Roentgentherapy is not discussed.

Disease and Its Causes. By W. T. COUNCILMAN, A. M., M. D., LL. D. (New York: Henry Holt & Co., 1913.)

This little volume published in a series known as the Home University Library of Modern Knowledge, should serve the useful purpose of giving the laity reliable information concerning the topic with which it deals. In about 250 pages Dr. Councilman defines disease and describes its extrinsic and intrinsic causes. A large portion of the book is devoted to a discussion of the infectious diseases, though other organic diseases, especially diseases of the heart, are briefly dealt with. The subject of insanity is also discussed and the relations of degeneracy and criminality to states of the nervous system touched upon. In the last chapter of the book the relation of modern conditions of life to the extension of disease is taken up.

We do not know of any other small volume in which the layman can find such a mass of information so clearly and attractively presented concerning the matters with which modern medicine has to deal.

Oxford Medical Manuals: The Elements of Bandaging, Fractures and Dislocations. By WILLIAM RANKIN, M. B. \$1.50. (London: Henry Frowde and Hodder & Stoughton, 1913.)

It is a small volume of 115 pages, with numerous illustrations and large type, so that the volume could be read easily in an hour. The three subjects discussed cannot be satisfactorily covered in such small compass, and it is to be regretted if the information contained is sufficient to prepare men "for the practical portion of their final examination."

Oxford Medical Publications: The Practitioner's Practical Prescriber. By D. M. MACDONALD, M. D. \$1.50.

Practical Presenting with Clinical Notes. By ARTHUR H. PRICHARD, M. R. C. S., etc. \$2. (London: Henry Frowde and Hodder & Stoughton, 1913.)

The first of these works is nothing more than a small pocket formulary to which is appended a table of dosage, brief directions for common emergencies, a pregnancy table, etc. The work is similar to many others, and will be useful to those who like this class of work.

Prichard's book is novel in its mode of presentation. He supplies a number of prescriptions, explains them by "giving, by way of explanatory notes, reasons for employing the various constituents, their particular actions, and any special points concern-

ing them. . . . to illustrate the effects of the various drugs in combination a number of illustrative cases have been epitomized. The results of treatment in these are indicated in short notes, while the main features of each case are briefly summed up by way of comment." The author arranges his remarks and clinical notes in parallel columns, and in this small volume he can only cover a limited field, but the method is one with distinct advantages, as it makes more vivid than usual the effect of drugs on patients. Though it is more adapted to the bedside than to book form, yet a good student will gain much from a careful reading of "Practical Presenting."

A Text-Book of Histology. By DR. FREDERIC T. LEWIS and DR. PHILIPP STÖHR. Second edition. Illustrated. \$3. (Philadelphia: P. Blakiston's Son & Co., 1914.)

A Text-Book of Histology. By FREDERICK R. BAILEY, M. D. Fourth revised edition. Illustrated. \$3.50. (New York: William Wood & Co., 1913.)

Stöhr's famous and most widely read work appears completely revised and much rewritten by Lewis, and it remains to be seen whether in its new form it will be as popular in the future as in the past. It is arranged upon an embryological basis, and as embryology now plays a much more important rôle in the medical curriculum than a few years ago, Lewis' book will be helpful for the student in association with his general anatomy.

The other histology, by Bailey, familiar to and liked by many students, will appeal readily to many more just beginning their study of medicine to whom it is well adapted by its clear style and simplicity.

The Practice of Medicine. By JAMES TYSON, M. D., etc., and M. HOWARD FUSSELL, M. D. Sixth edition. Revised and rewritten. Illustrated. (Philadelphia: P. Blackiston's Son & Co., 1914.)

The new edition has been abridged in parts and enlarged in others, causing imperfections as well as perfections. It is a pity that all the historical part of the subject had to be omitted, and also that the section on parasites, which are becoming more and more important in the study of medicine, had to be shortened. The work is more complete in having fuller accounts of some old diseases, and by the introduction of some diseases which are rare and not always included in all text-books of medicine. Otherwise this standard work remains unaltered, and noteworthy as the production of one of Philadelphia's eminent practitioners. The index is unfortunately incomplete; there is no reference, at least we could not find it, to phenosulphonephthalein, and yet this is mentioned as one of the important new subjects in the preface.

BOOKS RECEIVED.

Radium. As Employed in the Treatment of Cancer, Angiomata, Keloids, Local Tuberculosis and Other Affections. By Louis Wickham, M. V. O., and Paul Degrais. Translated by A. and A. G. Bateman, M. B., C. M. With fifty-three illustrations. 1913. 12°. 111 pages. Paul B. Hoeber, New York.

Modern Problems of Biology. Lectures delivered at the University of Jena, December, 1912. By Charles Sedgwick Minot. With fifty-three illustrations. 1913. 8°. 124 pages. P. Blakiston's Son & Co., Philadelphia.

Cancer of the Breast. An Experience of a Series of Operations and Their Results. By Charles Barrett Lockwood, F. R. C. S. (Eng.). 1913. 8vo. 234 pages. Henry Frowde, London; Hodder & Stoughton, London.

Treatment of Tuberculosis. Ordinary Therapeutics of Medical Men. By Albert Robin. Translated by Dr. Léon Blanc, with the assistance of H. de Méric. 1913. 8vo. 616 pages. The Macmillan Company, New York.

A Manual of Surgical Treatment. By Sir W. Watson Cheyne, Bart., C. B., D. Sc., LL. D., F. R. C. S., F. R. S., and F. F. Burgard, M. S. (Lond.), F. R. C. S. New edition, entirely revised and largely rewritten with the assistance of T. P. Legg, M. S. (Lond.), F. R. C. S., and Arthur Edmunds, M. S. (Lond.), F. R. C. S. Volume V. *The Treatment of the Surgical Affections of the Pancreas, Liver and Spleen, the Neck, the Breast and Thorax, and the Genito-Urinary Organs.* 1913. 8vo. 619 pages. Lea & Febiger, Philadelphia and New York.

Artificial Parthogenesis and Fertilization. By Jacques Loeb. Originally translated from the German by W. O. Redman King, B. A. Supplemented and revised by the author. [1913.] 8°. 312 pages. The University of Chicago Press, Chicago.

The Ideals and Organisation of a Medical Society. By Jamieson B. Hurry, M. A., M. D. 1913. 8°. 51 pages. J. & A. Churchill, London.

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JUL 1914

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THE INVOLUTION OF THE UTERUS AND ITS EFFECT UPON THE NITROGEN OUTPUT OF THE URINE.

By J. MORRIS SLEMONS,
Professor of Obstetrics and Gynecology, The University of California.

Some years ago I had the opportunity to study the nitrogenous metabolism of pregnant women who had been placed upon a constant diet containing about the same amount of nitrogen and possessing the same calorific value as that the average woman would select. Similar observations were made during labor and continued for three weeks in the puerperium. The total nitrogen curve of the urine, thus obtained, presented three main features. During the latter part of pregnancy it was lower than in non-pregnant women; at the time of labor it fell even below the level of pregnancy; while during the puerperium it rose to such an extent as to become greater than that generally accepted as normal. This relatively high excretion persisted for about two weeks.

At the time my results were published their explanation could be only a matter of conjecture. The retention of nitrogen during pregnancy, it seemed, must be in the interest of the fetus, as it was needed to assist in its growth as well as to promote the development of the uterus, the placenta, the breasts, and other organs which function more actively during or just after pregnancy. The nutritional requirements of the maternal organs which subserve the welfare of the fetus are not inconsiderable; and Landsberg estimates that the amount of nitrogen retained during pregnancy is four times greater than is necessary for fetal growth alone. These factors in the retention of nitrogen during pregnancy have been accepted by

all who have investigated the subject, notably by Zacherjewsky, Schrader, Sillevis, Hahl, Bar, Murlin and Bailey, Hoffström and Seitz, but as yet no one has discovered the mechanism by which such a retention is effected.

The low urinary excretion at the time of labor also remains unexplained. It may result from a disturbance in the renal circulation, for which the uterine contractions are primarily responsible, or from the effect upon the kidneys of some as yet unknown metabolic product, which simultaneously stimulates the uterus to contract, and in all probability is due to a combination of these factors.

The increase in the excretion of nitrogen through the urine, which is regularly observed after labor, has given rise to a good deal of speculation; and several hypothetical explanations have been advanced concerning it. Grammatikati thought that it was due to lactation, and based his belief upon the theory that the fat in the milk was formed from protein. In this event the nitrogenous residue became a waste-product, and its elimination through the kidneys would account for the large increase in the amount of nitrogen in the mother's urine. While it is impossible to prove that this theory of the formation of milk-fat is incorrect, no evidence has been adduced to show that lactation is responsible for the large nitrogenous excretion through the urine of puerperal women. On the contrary, all the evidence is against it, as the phenomenon appears even

though the woman does not suckle her baby. Furthermore, when lactation continues undisturbed, the nitrogen output diminishes about the end of the second week after labor. Likewise, the suggestion which holds that too sparse a diet is responsible for the phenomenon is equally untenable, as puerperal women who receive an amount of nourishment quite sufficient for their weight still excrete an unusually large quantity of nitrogen during the first two weeks of the lying-in period.

The correct explanation is very simple. Purely upon clinical grounds it would seem probable that the phenomenon is associated with the involution of the uterus—a process by which the organ is reduced within a few weeks from the size of a newborn baby's head to that of its fist, while its weight becomes diminished from 1000 to 50 or 60 grammes. The process is now regarded as due to autolysis which breaks the muscle-protein down into simpler substances. These pass into the circulation, are eliminated through the kidneys, and thus increase the amount of nitrogen in the urine.

Fortunately, this hypothesis can be tested experimentally, and requires two series of observations. In the first we ascertain whether the increased nitrogenous output observed after normal labor is in any way affected by the performance of Cæsarean section; while in the second we determine whether it is influenced by the removal of the uterus at the time Cæsarean section is performed. If there is a marked decrease in the amount of nitrogen excreted after the removal of the uterus, it would appear justifiable to attribute it to the artificial interference with involution. The opportunity to investigate this problem was given me by Doctor J. Whitridge Williams while I was a member of the staff of The Johns Hopkins Hospital, and the records of two cases in which the observations were most complete form the basis of this report.

CASE I. CONSERVATIVE CÆSAREAN SECTION.

A. W., negress, II para, 31 years old, generally contracted rachitic pelvis, pregnancy normal, expected date of confinement, February 8.

Labor began February 12 and lasted 46½ hours, when a classical Cæsarean section was performed. Ether anæsthesia lasted one hour. The puerperium was normal until the 23d day, when a small superficial breast abscess developed, which was promptly incised and healed within a week.

Metabolic observations were begun 32 days before delivery. At that time the patient's weight was 119¾ lbs., and ten days later 122¾ lbs. During this period the average daily nitrogenous content of the food was 15.6 gm., of the urine 10.23 gm., of the feces 1.68 gm. The average daily storage of nitrogen was 3.66 gm.

On the day of delivery the fluid intake was 730 cc. and the urine measured 890 cc. The nitrogen of the food was 4.38 gm., of the urine 5.04 gm. The patient weighed 110 lbs. at the conclusion of the operation.

Liquid nourishment alone was permitted for three days after operation and the diet used during pregnancy was not again employed until the end of a week. During the first 20 days of the puerperium the average daily nitrogen of the food was 12.88 gm., of the urine 12.15 gm. The additional loss through the milk, lochia, and feces resulted in a negative nitrogen balance, so that the average daily loss of nitrogen was 3.56 gm. At the end of this period the patient weighed 105 lbs.

From clinical observation of the size of the uterus, as well as from the character of the urinary nitrogen curve, it seemed that the acute involution of the uterus ended about the 17th day. Observations, however, were continued until the 21st day, when the patient complained of pain in the breast. The temperature was then 100.5° F., and two days later rose to 104.5° F. It fell to normal shortly after the abscess was opened. Although the urine was collected and analysed during the existence of this complication, the results are not included here, for the high nitrogen values obtained were due to the fever, and bear no relation to the problem under investigation.

Observations were resumed after the patient had entirely recovered, namely, from the 41st to the 45th day postpartum. The diet was then the same as had been employed during pregnancy. The urine nitrogen averaged 10.25 gm. per day. During this period the patient was practically in nitrogenous equilibrium. She weighed 107 lbs. at the beginning and 107¼ lbs. at the end of this, the final series of observations.

CASE II. CÆSAREAN SECTION WITH SUPRAVAGINAL HYSTERECTOMY.

S. C., negress, I para, 21 years old, pregnancy normal, expected date of confinement, July 29.

Labor began July 27, and shortly after its onset a Porro Cæsarean section was performed. Ether anæsthesia lasted an hour and a quarter. The puerperium was normal, but the patient was unable to nurse the baby satisfactorily on account of an inadequate supply of milk.

Metabolic observations were made uninterruptedly from the 14th day before delivery until the 20th day postpartum. Since the decision to perform Cæsarean section had been reached in advance, it was possible to do the operation at the close of one of the 24-hour periods of observation. On this account the data designated the day before delivery actually includes several hours after labor had begun.

At the beginning of the observations the patient weighed 96 lbs., and at the onset of labor 99½ lbs. Unusually satisfactory data were obtained during the 11 days of pregnancy while the patient was taking a mixed diet. At the end of that time observations were desired relating to a liquid diet such as would probably be used for some days after the operation. These were in progress when labor started.

During the last two weeks of pregnancy the average daily nitrogenous content of the food was 15.02 gm., of the urine 8.70 gm., and of the feces 1.8 gm. The average daily storage of nitrogen was 4.52 gm.

Although the diet for two days following the operation consisted of liquids in restricted amounts, the output of nitrogen through the urine rose immediately and reached its maximum on the 3d day postpartum. An attempt was made to return to the diet which had been used during pregnancy, but the patient was unable to take so much, and was not able to do so until the end of two weeks.

During the puerperium the average daily amount of nitrogen in the food was 12.59 gm., in the urine 9.10 gm., and in the feces 0.95 gm. The patient did not suckle her baby and there was no lochia. The nitrogen balance was negative four days after operation, but subsequently was positive. The average daily retention was 2.45 gm. nitrogen. The patient weighed 79½ lbs. just after the operation, and 84¾ lbs. at the conclusion of the postpartum observations.

The body of the uterus removed at the Cæsarean section weighed 850 gm. A small portion of the fresh tissue was dried to constant weight and showed that 70 per cent moisture was present. Consequently the amount of water-free substance in the entire uterus was 255 gm. Analysis by the Kjeldahl method showed that the uterus contained 38.75 gm. of nitrogen.

These observations show in the first place that after Cesarean section the output of urinary nitrogen is high. For example, the excretion in Case I rose on the 3d day and remained elevated for about two weeks. During this period the involution of the uterus was in progress; it was probably completed on the 17th day, certainly not later than the 20th day. The average daily excretion for this period was 1.9 grams greater than during the postpuerperal period. In other words, about 40 grams of urinary nitrogen excreted during the first 20 days of the puerperium must be accounted for, and this is also the problem presented in the case of women who have been delivered naturally.

With regard to a few minor points, the puerperal metabolism of this patient did not follow the rule. Thus, the increase in the output of nitrogen began somewhat later and continued somewhat longer than usual, and also reached a greater maximum elevation than we are accustomed to see in the normal puerperium. Such deviations, however, may be explained by the influence of the anæsthetic and by the fact that the patient was

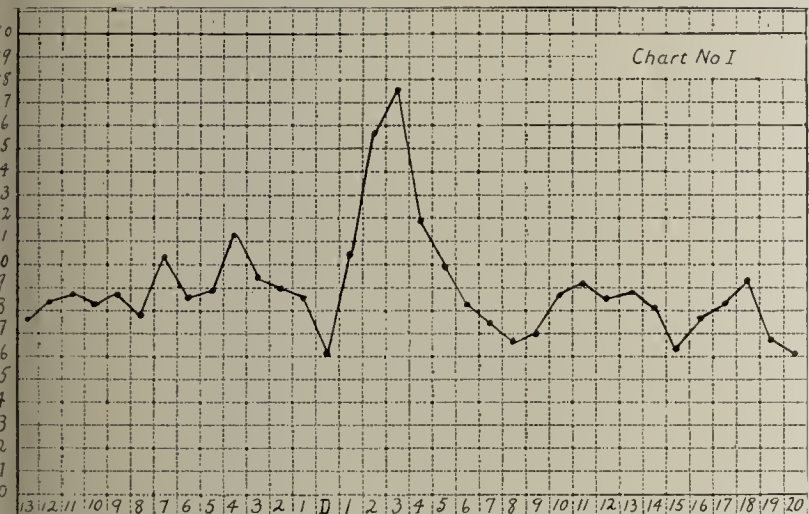


CHART I.—The total nitrogen of the urine during pregnancy and the puerperium in Case II in which Porro Cesarean section was performed. Figures at the side represent gm. of nitrogen, those at the bottom the day before or after delivery. (D) is the day of operation.

recovering from a laparotomy. The latter influence probably delays involution, as do other puerperal complications which have been considered in detail by Dittrich, Goodall and others.

In both Cases I and II the most conspicuous feature of the nitrogen excretion is the sharp rise following the operation, but this feature is not entirely attributable to conditions peculiar to pregnancy or the puerperium. A similar increase in the urinary nitrogen may occur after operations upon women who are not pregnant as well as after operations upon men. Moreover, it may occur after the administration of an anæsthetic merely for diagnostic purposes.

The effect of chloroform and of ether anæsthesia upon the excretion of nitrogen has been studied both clinically and experimentally. Thus Vidal found after anæsthetizing dogs with chloroform that the urine contained two or three times as much nitrogen as normal. Similar experiments by Strassmann revealed an increase of 20 per cent. Drapier, however, whose observations were made upon human beings, noted a less

marked increase and stated that the increase in the nitrogen immediately after chloroform narcosis might be so slight as to be obscured in the 24-hour urine.

A similar increase in the urinary nitrogen following ether anæsthesia has been described by Kappeler, Leppmann, Hawk, and others. The carefully conducted experiments made upon dogs by Hawk show that after ether narcosis the urine presents an increase in nitrogen amounting to from 6.5 to 27.1 per cent. From not altogether sufficient evidence Hawk considers that the duration of anæsthesia bears no relation to the amount of nitrogen lost, and believes that the susceptibility of the individual must account for such differences as he noted. In exceptional instances he found no change in the excretion, but as a rule within 48 hours after ether anæsthesia the urinary nitrogen rose and remained high for a day or so, occasionally for as long as five or six days.

Observations which I have made upon gynecological patients show that anæsthesia has the same effect as was noted in animal experiments. Following operation there is generally, though not invariably, an increase in the urinary nitrogen. Moreover,

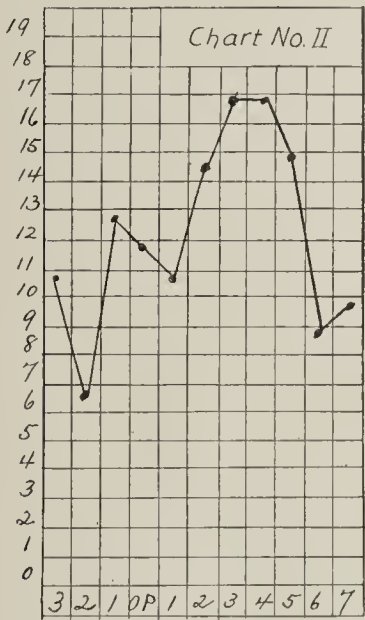


CHART II.—The total nitrogen of the urine before and after suspension of the uterus. Duration of anæsthesia one hour. Figures at the side represent gm. of nitrogen, those at the bottom the days preceding or following operation.

the phenomenon is independent of the diet, of hæmorrhage, and of the absorption of blood from the peritoneal cavity. I am, however, inclined to believe that the duration of anæsthesia may be a factor of importance, for the increase is less pronounced when the anæsthesia is brief, as in cases of curettage, than in longer operations.

To illustrate the increase which may occur in the urinary nitrogen following an uncomplicated laparotomy, it will suffice to give the records of a patient upon whom ventro-suspension of the uterus was performed. This patient took the same amount of nourishment each day except during the day of operation; and her diet of milk, bread, and rice contained 12 grams of nitrogen. The urinary nitrogen, which is represented in Chart II, was notably higher from the 2d to the 5th days following operation; and this result can be attributed only to

the influence of the anæsthetic, for the dietary conditions were identical before and after operation and there was practically no loss of blood.

In view of the experimental and clinical evidence here adduced there can be no doubt that the rise in the urinary nitrogen immediately following the Porro Cæsarean section is referable to the influence of anæsthesia. In Case I, as well, there was a similar effect, but the presence of the involuting uterus makes it impossible to estimate exactly the influence of the anæsthetic. Certain other facts, however, are of interest. Thus, the effect of anæsthesia became evident more promptly in the case from which the uterus had been removed. On the other hand, both the maximum daily excretion and the average excretion were greater in the case of conservative section, which must have been due to the fact that the uterus was in process of involution.

In further comparing our cases, however, the effect of anæsthesia may be disregarded, since both were subject to its influ-

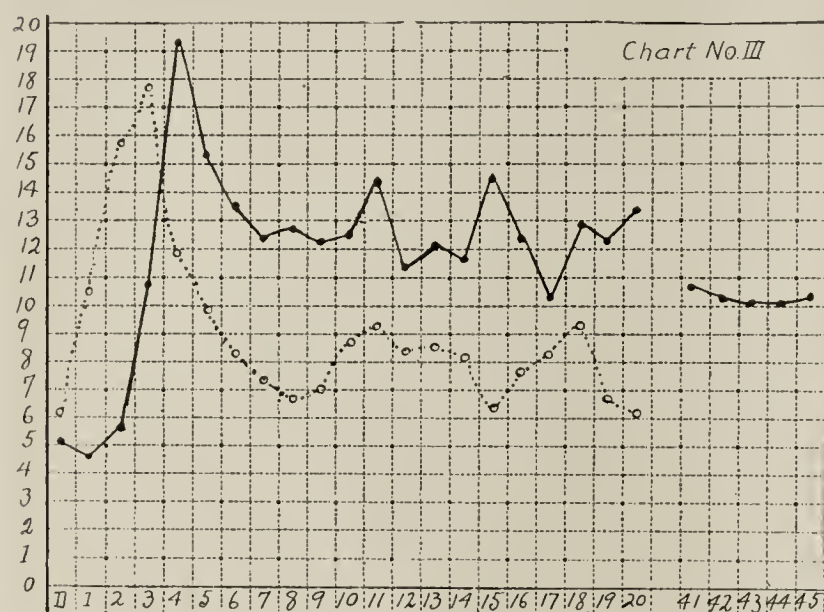


CHART III.—Contrasting the total nitrogen of the urine after conservative Cæsarean section and after the Porro operation. Solid line represents the excretion in Case I, in which the uterus was not removed; broken line that of Case II, in which it was removed. Figures at the side and bottom have same significance as in other charts.

ence. The period chosen as the basis of comparison, naturally, would be determined by the duration of the involution process in the case in which the uterus was not removed, and in order to be sure that the records covered this period, observations were continued for the first 20 days of the puerperium. During this time there was a difference of 61 grams between the aggregate amounts of nitrogen eliminated by the two patients, an average daily difference of 3 grams, and it is upon the latter figure that stress should chiefly be laid. Furthermore, I feel that emphasis should be laid not so much upon the actual amount of difference, which might well vary when other individuals were subjected to similar observations, but upon the fact that a tangible difference existed and that a larger excretion occurred when the uterus was not removed.

A significant result of my observations is that the excessive excretion in Case I, amounting to 61 grams, counterbalances

the nitrogenous content of the uterus of the other patient. In fact, it more than does so, for the organ contained only 38.25 grams of nitrogen. This disparity of 22 grams, however, is within the limit of experimental error, when conditions must be met such as are encountered in the study of this problem.

It is perhaps unnecessary to point out that ideal experiments would require that one should have pregnant women of equal weight, with similar appetites, with identical powers of recuperation after operation, and with the fortitude to remain on the same diet for a period of a month. In such circumstances mathematical precision might be hoped for, and probably would be more nearly attained; but such a favorable opportunity is not likely to present itself. And the disparity is not a large one, for it amounts roundly to 1 gram of nitrogen per day; or, in other words, to a half gram per day for each patient. Furthermore, observations upon other women whose uteri were removed at the time of Cæsarean section confirm the results presented by Case II. The data given in the following table indicate that when the uterus is removed the subsequent excretion of urinary nitrogen is regularly less than when the uterus is preserved.

DAILY AVERAGE NITROGEN OF THE URINE.

(1) After Porro Cæsarean Section:

S. C. (observed 20 days)..... 9.10 gm.

J. J. (observed 16 days)..... 10.92 gm.

A. J. (observed 10 days)..... 8.92 gm.

(2) After Conservative Cæsarean Section:

A. W. (observed 20 days)..... 12.15 gm.

In the normal puerperium the involution of the uterus begins immediately after delivery and occupies about six weeks, but the acute period is practically completed by the end of the second week. The latter estimate would seem correct when judged from several points of view. For example, clinical observation of the decrease in the size of the organ indicates that the major part of the process is effected during this period, while the mensuration of the individual muscle-fibres by Säger on consecutive days throughout the process justify a similar conclusion. Furthermore, metabolic observations upon normal puerperal women indicate that the excretion of the nitrogenous products of involution is practically completed during the first two weeks of the puerperium. Consequently, if this be the period of acute involution, and if the amount of nitrogen lost from the body in consequence of the process corresponds to the nitrogenous content of the uterus removed at the time of delivery and before the commencement of involutionary changes, it must follow that the theoretical loss of nitrogen per day should be from 2 to 3 grams. Upon comparison of this estimate with the average daily difference (3.05 grams) actually found to exist in Cases I and II, one must conclude that the excessive excretion after the conservative Cæsarean section is due to the involution of the uterus. To be sure, in the case in which the uterus was removed the nitrogen output was greater for three days, but this is readily explained as a result of the anæsthesia. After this period, however, the output was greater in the case in which the uterus was undergoing involution.

COMPARISON OF TOTAL NITROGEN OF URINE AFTER CONSERVATIVE AND PORRO CÆSAREAN.

Day.	1.	2.	3.	4.	5.	6.	7.	8.
Case I.	4.70	5.49	10.90	19.15	15.19	13.48	12.37	12.79
Case II.	10.50	15.73	17.64	11.90	9.90	8.28	7.40	6.67
Difference ..	+5.80	+10.24	+6.74	-7.25	-5.29	-5.20	-4.97	-6.12
Day.	9.	10.	11.	12.	13.	14.	15.	16.
Case I.	12.35	12.64	14.26	11.34	12.08	11.80	14.46	12.25
Case II.	7.02	8.64	9.10	8.40	8.60	8.10	6.30	7.65
Difference ..	-5.33	-4.00	-5.16	-2.94	-3.48	-3.70	-8.16	-4.60
Day.	17.	18.	19.	20.	Total.	Daily average.		
Case I.	10.28	12.91	12.32	13.32	243.04	12.15		
Case II.	8.31	9.20	6.56	6.13	182.03	9.10		
Difference ..	-1.97	-3.71	-5.76	-7.19	-61.01	-3.05		

As the result of my investigations, it is apparent that the process of involution causes a rise in the urinary nitrogen and that the amount of excessive elimination corresponds to the nitrogenous content of the non-involuted uterus. My observations offer confirmatory evidence of this fact from three points of view: First, by the comparison of the puerperal and postpuerperal periods when the uterus has not been removed; secondly, from the comparison of the aggregate excretion in cases in which the uterus was removed and in which it was not; and, thirdly, from the comparison of the actual daily difference in such cases with the theoretical amount of nitrogen which would be expected as a result of the involutionary process. We may, therefore, conclude that waste-products from the involuting uterus pass into the circulation, are excreted by the kidneys, and in some measure throw additional work upon these organs during the early part of the puerperium.

It does not follow, however, that the diet should be restricted in the puerperium. On the contrary, our observations indicate that the increase in the excretion of nitrogen is not large enough to require such restriction, provided the patient is normal. If any therapeutic inference may be drawn, it is in the nature of a justification of the present-day tendency to allow a generous diet to recently delivered women.

On the other hand, in patients suffering from toxæmia of pregnancy, the additional work which the kidneys must perform in the puerperium does become a matter of practical importance. In such circumstances these organs should be given the fullest opportunity to recover from the strain to which they have been subjected, and, with this end in view, the diet should be limited. Such precaution is necessary, not only because the renal cells have been damaged, but also because an excretory capacity somewhat greater than normal is desirable.

The inspection of the urine-chart of a convalescent eclamptic teaches that in the days immediately following delivery the kidneys are eliminating an unusually large amount of waste-products, even though the consumption of food is small. Formerly, the large nitrogenous excretion in such cases was attributed to the elimination of waste-material which had previously been retained, and whose retention had caused the toxæmia. Such a view is evidently incorrect, as my observations show that the large excretion of nitrogen in these, as well as in normal cases, is due to the involution of the uterus.

TABULATION OF DATA.

CASE I. (A. W.) CONSERVATIVE CÆSAREAN SECTION.
(Uterus not removed.)

OBSERVATIONS DURING PREGNANCY.

Day before delivery.	Fluid by mouth.	Quantity of urine.	Nitrogen of food.	Nitrogen of urine.	Nitrogen of feces.	Nitrogen balance.	Weight of pt.
	cc.	cc.	gm.	gm.	gm.		lbs.
32	1755	775	14.91	6.98	1.68	+6.25	119 ³ / ₄
31	1755	900	15.00	9.00	1.68	+4.32
30	1755	1150	15.00	10.58	1.68	+2.74
29	1755	750	15.00	8.25	1.68	+5.07
28	1630	1325	17.30	13.25	1.68	+2.37
27	1630	860	15.70	9.48	1.68	+4.54
26	1630	675	15.70	7.44	1.68	+6.58
25	1440	1000	15.70	13.16	1.68	+0.86
24	1440	1000	15.70	10.60	1.68	+3.42
23	1440	900	15.70	13.60	1.68	+0.42	122 ¹ / ₂
Daily average.	1619	933	15.6	10.23	1.68	+3.66

OBSERVATIONS DURING PUERPERIUM.

Day after delivery.	Fluid by mouth.	Quantity of urine.	Nitrogen of food.	Nitrogen of urine.	Nitrogen of feces.	Nitrogen of milk.	Nitrogen of lochia.	Nitrogen balance.	Weight of pt.
	cc.	cc.	gm.	gm.	gm.	gm.	gm.		lbs.
1	367	300	2.63	4.70	1.20	0	1.8	-6.07	110
2	460	400	1.25	5.49	1.20	0	1.5	-6.94	...
3	1665	600	7.56	10.90	1.20	0	1.7	-6.24	...
4	2065	850	15.06	19.15	1.20	0	0.9	-8.39	...
5	1995	1085	12.33	15.19	1.20	2.2	0.5	-8.16	...
6	1670	1070	9.90	13.48	1.20	2.6	...	-7.98	...
7	1850	950	12.67	12.37	1.20	4.1	...	-5.00	...
8	2640	1100	15.10	12.79	1.20	3.6	...	-2.49	...
9	2680	1390	15.10	12.35	1.20	1.6	...	-0.05	...
10	2480	950	15.10	12.64	1.20	1.9	...	-0.64	...
11	2350	1350	15.10	14.26	1.20	1.4	...	-1.76	...
12	2380	1350	15.10	11.34	1.20	3.1	...	-0.54	...
13	1990	1570	15.10	12.08	1.20	1.9	...	-0.08	...
14	2300	1290	15.10	11.80	1.20	1.7	...	+0.40	...
15	2340	1270	15.10	14.46	1.20	6.3	...	-2.66	...
16	2300	1250	15.10	12.25	1.20	2.1	...	-0.45	...
17	2780	1450	15.10	10.28	1.20	5.6	...	-1.98	...
18	2940	2100	15.10	12.91	1.20	3.0	...	-2.01	...
19	3320	2200	15.10	12.32	1.20	6.0	...	-4.42	...
20	2820	1850	15.10	13.32	1.20	6.4	...	-5.82	105
Daily av'ge.	2119	1220	12.88	12.15	1.20	3.3	...	-3.56	...
41	1620	1300	15.70	10.56	1.45	4.9	...	-1.21	107
42	1620	1500	15.70	10.20	1.45	3.9	...	+0.15	...
43	1620	1600	15.70	10.08	1.45	4.4	...	-0.23	...
44	1620	1225	15.70	10.04	1.45	4.4	...	-0.19	...
45	1620	1300	15.70	10.40	1.45	4.1	...	-0.25	107 ¹ / ₂
Daily av'ge.	1620	1385	15.70	10.25	1.45	4.3	...	-0.34	...

CASE II. (S. C.) PORRO CÆSAREAN SECTION.
(Uterus removed.)

OBSERVATIONS DURING PREGNANCY.

Day before delivery.	Fluid by mouth.	Quantity of urine.	Nitrogen of food.	Nitrogen of urine.	Nitrogen of feces.	Nitrogen balance.	Weight of pt.
	cc.	cc.	gm.	gm.	gm.		lbs.
14	1550	1150	15.70	7.60	1.8	+6.30	96
13	1580	1150	15.70	8.28	1.8	+5.62	..
12	1580	800	15.70	8.78	1.8	+5.12	..
11	1580	625	15.70	8.31	1.8	+5.59	..
10	1580	700	15.70	8.82	1.8	+5.08	..
9	1580	600	15.70	7.88	1.8	+6.02	..
8	1580	900	15.70	10.33	1.8	+3.57	..
7	1580	950	15.70	8.65	1.8	+5.25	..
6	1580	1100	15.70	8.96	1.8	+4.94	..
5	1580	1500	15.70	11.24	1.8	+2.66	..
4	1580	1350	15.70	9.45	1.8	+4.45	..
3	2880	2250	13.89	9.00	1.8	+3.09	..
2	2880	1800	13.89	8.46	1.8	+3.63	..
1	1760	1200	9.90	6.05	1.8	+2.05	99½
Daily average.	1776	1148	15.02	8.70	1.8	+4.52	

OBSERVATIONS DURING PUERPERIUM.

1	725	600	4.41	10.50	0.95	-7.03	
2	1510	725	9.14	15.73	0.95	-7.54	79½
3	2480	900	12.00	17.64	0.95	-6.59	...
4	2480	850	12.00	11.90	0.95	-0.85	...
5	2480	1650	12.00	9.90	0.95	+1.15	...
6	2480	1800	12.00	8.28	0.95	+2.77	...
7	2480	1850	12.00	7.40	0.95	+3.65	...
8	2480	1450	12.00	6.67	0.95	+4.38	...
9	2480	1350	12.00	7.02	0.95	+4.03	...
10	2480	1200	12.00	8.64	0.95	+2.41	...
11	2480	1450	12.00	9.10	0.95	+1.95	...
12	2480	1600	12.00	8.40	0.95	+2.65	...
13	2480	1750	12.00	8.60	0.95	+2.45	...
14	2480	1650	12.00	8.10	0.95	+2.95	...
15	1580	850	15.70	6.30	0.95	+6.65	...
16	1580	950	15.70	7.65	0.95	+7.10	...
17	1580	1250	15.70	8.31	0.95	+6.44	...
18	1580	1150	15.70	9.20	0.95	+5.55	...
19	1580	1250	15.70	6.56	0.95	+8.19	...
20	1580	1250	15.70	6.13	0.95	+8.62	84¾
Daily average.	2074	1126	12.59	9.10	0.95	+2.45	

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THE NORMAL AMOUNT OF DIASTATIC FERMENT IN THE FECES
AND ITS VARIATION IN CERTAIN DISEASES OF THE
PANCREAS AND IN ACHYLIA GASTRICA.

By THOMAS R. BROWN, M. D., Baltimore, Md.

(From the Chemical Laboratory of the Medical Clinic.)

We have studied quantitatively the diastase in the feces in the hope that by establishing the normal limit, especially the low normal, we might have criteria of value in the diagnosis of organic or functional diseases of the pancreas, determining whether or no in such diseases a definite variation from the normal is constantly found. We have chosen the diastase in preference to the trypsin or lipase because of its greater sta-

bility, because the trypsin digestion may be simulated by the action of erepsin, because of the marked proteolytic action of the bacteria, much more striking than their diastatic action, because practically all the diastase that is secreted into the intestinal tract arises from the pancreas, the amount from Brunner's glands and gall-bladder, the only other sources, in all probability being so small in amount as to be practically

negligible, and because it is a preformed ferment, and does not require an activator.

We have attempted to devise a method which is simple, practical and exact, and based on physiological principles, and by applying the same method to normal and pathological conditions to draw comparisons of value in diagnosis. In practically all the diseased conditions the diagnosis was verified by operation.

Of course a great many methods have been suggested as qualitative and a few as quantitative tests of the pancreatic function—Sahli's glintoid capsule, Müller and Schlecht's gelodurot capsule, the study of the stool for large amounts of meat and fat—creatorrhœa and stercorrhœa—after the Schmidt diet, the Volhard method of obtaining the duodenal contents from the stomach by administering olive oil by mouth and the examination of the fluid for the pancreatic ferment, Ehrmann's palmitin test, Einhorn's intubation of the duodenum, A. Schmidt's nuclei test, the Cammidge reaction, and the alimentary glycosuria test being among those suggested. None of these is definitely quantitative, however, and for this purpose the estimation of the pancreatic ferment in the stools suggests itself. Of these ferments the trypsin and lipase are more easily destroyed by bacteria, the former is almost similar in action to erepsin, each requires activation to show their maximum efficiency, the former by enterokinase, the latter by bile, and the proteolytic action of the intestinal bacteria may complicate the findings very markedly.

We have, therefore, chosen diastase as the ferment to be estimated, and the fact that it is more stable, that it comes preformed and does not require an activator, and that with the exception of a minimal amount supplied by the secretion from Brunner's glands and the bile its sole source of supply to the intestine is the pancreas, makes it the logical choice.

Of course, in all such estimations the salivary diastase—identical in action with that from the pancreas—must be eliminated, but this is easily done by administering a food in liquid form in which the act of chewing is not called into play. Of the other ferments found in the small intestines, erepsin, peptolytic ferment, nuclease, lipase, fibrin ferment, hemolysin and gloeoside—splitting ferment, none appreciably affects the action of the diastase. This action, of course, is the conversion of starch to maltose, the intermediary products being soluble starch, erythrodextrin, achroodextrin, and isomaltose.

The only justification for an attempt to quantitatively estimate the pancreatic ferments is the fact that many animal and a few human experiments (patients with a pancreatic fistula) have shown that there is definite quantitative as well as qualitative response on the part of the pancreas to the quantity and character of the food ingested. Even in 1677 de Graaf studied the action of the pancreas by establishing a pancreatic fistula in a dog, a method subsequently employed by Claude Bernard, who demonstrated the activating effect of ether on the gland's secretion, but it was, of course, Pawlow who demonstrated the fact that there was a definite quantitative relationship between amount and character of food

and amount and character of juice, his classical experiments on dogs having been verified by numbers of investigations since. His experiments, such as the one that after 600 cc. of milk a dog secreted 9 cc. of pancreatic juice in the first hour, 7 cc. in the second, 23 cc. in the third, 9 cc. in the fourth, and 2 cc. in the fifth, and that there was a definite and exact relationship between amount of milk given and amount of juice secreted, should be mentioned in this connection. As to the mechanism of this secretion, there has been and still is a considerable difference of opinion. Pawlow believed that it was a nervous reflex through the cortex, Popielski that it was a local nervous reflex through the ganglion cells in the pancreas, while, according to Starling, "the formation of hormones and their circulation through the blood to the reactive tissue suffices to account for the whole activity of the gland, and it is doubtful whether in this activity the nervous system plays any part whatsoever." According to Bayliss and Starling, this hormone, secretin, is produced by the action of the hydrochloric acid of the stomach upon the prosecretin found in the duodenal mucous membrane; other acids, acetic, lactic, etc., however, have a similar effect. According to Cohnheim, the action of acids upon the duodenum, psychic stimuli, as the smell, taste or sight of food, and fats, fatty acids and soaps, all act as stimulants to pancreatic secretion. According to Wohlgemuth¹ the action of the fat is both reflex and humoral, while he and other observers have proven the activating effect of various other substances upon the pancreatic secretion, such as peptones, alcohol, sodium chloride, lipoids, lecithin, etc. Of special interest is the activating influence of bile upon the pancreatic juice. We have entered into the various views held as to the physiology of pancreatic secretion, as it is of special interest in the interpretation of certain of our findings, notably those in achylia gastrica.

As to the methods described for studying the diastase in the stool to determine the pancreatic function, most are based on the same principle, the conversion of starch into lower products which do not give the characteristic starch reaction with iodine, or the determination of the sugar produced by this cleavage by Fehling's solution or some other reagent. Roberts, Strasburger,² Wohlgemuth³ and Ed. Müller⁴ all describe such methods—the results, however, are open to serious criticism because they used different foods, and various or no laxatives, and thus rendered possible enormous variations in the diastase content of the stool. Diarrhœa always increases the stool diastase, constipation lessens it, while Ury⁵ has shown that of the purgatives senna really increases the diastase in the stool, while the bitter waters and bitter salts have no such effect. It would seem wise, therefore, to choose a bitter salt as a laxative of choice in these investigations.

¹ Berl. klin. Wchnschr., 1908, XLV, 389; Biochem. Ztschr., 1909, XXI, 447, and 1911, XXXIII, 303.

² Deutsches Arch. f. klin. Med., 1909, LXXVII, 238.

³ Biochem. Ztschr., 1908, IX, 1.

⁴ Zentralbl. f. inn. Med., 1908, XXIX, 385.

⁵ Biochem. Ztschr., 1909, XXIII, 153.

Enriquez, Ambard, and Binet⁶ and Durand⁷ reported a number of cases in which the digestion of starch was measured by the quantitative estimation of the sugar formed and by giving the same diet, milk, the same laxative, sulphate of soda, and by diluting the stool to the same extent minimized the errors inherent in any method not taking these factors into account. We, however, regard the Wohlgemuth test for diastase as far more practical than the quantitative estimation of the sugar formed, and quite as free from criticism on theoretical grounds. As for the results of these quantitative studies, Wynhausen⁸ found that in most cases it varied between 500 and 20,000 units; Arnold⁹ between 312 and 2000. Rotky¹⁰ thought that the study of the desiccated stool was the only satisfactory method, and that by this method there is not a very great deviation in normal cases. Durand found by the method of Enriquez a variation between 14.3 and 48 units of diastase in the normal stool, the units, of course, being different here from those mentioned above. No discussion of the ferment content of the stool would be complete without a reference to the very extensive and interesting studies of Crohn¹¹ in this connection. Although devoting the major portion of his investigations to the study of the duodenal fluid, he has also studied the ferments in the stool. He did not employ cathartics and used either a fresh night or early morning specimen. In the case of both duodenal fluid and stool he gives a table of normal variations for the three ferments, lipase, trypsin, and diastase, and of these three he believes trypsin is the most constant. He believes that the method lends itself to prognosticating qualitative and quantitative variations in the strength of the pancreatic external secretion.

In the methods employed by us in determining the normal amount of diastase in the stool we have tried to eliminate as far as possible all sources of error, and to so standardize the different steps that mistakes would be reduced to a minimum. The patient was given a high enema the night before, the evening meal being a very light one. At 7 a. m. the next day 750 cc. of milk were given, at 7.30 a. m., and again at 8 a. m., $\frac{1}{2}$ an ounce of Epsom salts ($Mg SO_4$), and at 8.30 a. m. a glass of water containing $\frac{1}{4}$ of a teaspoonful of bicarbonate of soda. All the stool up to 2 p. m. was saved in a vessel containing two ounces of toluol, and kept on the ice or in a cool room. If less than 400 grammes or cubic centimeters of stool were obtained an enema of a pint of water was given, as in our experience between 400 and 1100 cc. of stool was the amount to be expected in the individual case.

Barring the inevitable possible mistakes always associated with the gathering of specimens, the possible sources of error are psychic variations in the different patients, differences in

their intestinal bacterial flora, and variations in the motor functions of their stomach and intestines, but we believe these inevitable sources of error are reduced to a minimum by the method employed.

The stool was examined as soon as possible, diluted up to 3000 cc. with normal salt solution, stirred until absolutely homogeneous, a portion centrifugalized for 5 minutes and the supernatant fairly clear fluid used for the tests.

Diminishing amounts of this fluid were put into a series of tubes, 1.8 cc. in the first, 1.6 cc. in the second, 1.4 cc. in the third, 1.2 cc. in the fourth, 1 cc. in the fifth, 0.8 cc. in the sixth, 0.6 cc. in the seventh, 0.4 cc. in the eighth, 0.2 cc. in the ninth, 0.1 cc. in the tenth, 0.05 cc. in the eleventh, and 0.025 in the twelfth, and the fluid in each of the tubes brought up to 2 cc. with normal salt solution. If the test showed a negative result in the first tube, or if we suspected very low readings, we used a supplementary series of tubes containing respectively 2 cc., 3 cc., 4 cc. and 5 cc. of the centrifugalized mixture. To each of the tubes were added 2 cc. of 1 per cent solution of soluble starch (Kahlbaum), the tubes were then incubated at 38° C. in a water bath for $\frac{1}{2}$ an hour, cooled by the addition of tap water, and by placing them under the cool tap, and tested quickly with a few drops of 1/10 normal iodine solution, the limit being that tube before the one in which the first definite blue color appears. As in the case of the urine, slight variations in the temperature of the water bath and in the reaction of the medium had very little influence upon the readings, and we, therefore, did not regard it as necessary to reduce all the specimens to the same degree of reaction to litmus. In a few of our earlier cases the stool-fluid in the tubes was reduced in geometrical instead of arithmetical progression. The results obtained in 15 normal adult cases, men and women being about equally represented (our unit being the digestion of 1 cc. of 1 per cent starch solution at 38° C. in $\frac{1}{2}$ hour), were as follows: In three cases 60,000 units; in two, 80,000; in one, 100,000; in seven, 120,000; in one, 140,000, and in two, 240,000. Of course, this means that there was no starch left in the tube corresponding to these units, and the exact figures, of course, would be somewhere between this and the next succeeding tube. The low normal reading in our series, therefore, was tube 10 or 60,000 units. Expressed in the units used by some others, that is the total amount of starch which would be digested by the whole stool (in $\frac{1}{2}$ an hour in the water bath at 38° C.), this would make the limits of our normal readings 600 units to 2400 units, although it is possible that higher figures for the high normal would be obtained if we carried our series of tubes to greater dilutions, but we were especially interested in obtaining a low normal, and this, if one can judge from 15 cases, we have obtained.

Using the same method we have studied a small group of cases of carcinoma of the pancreas and chronic pancreatitis, in most of which the diagnosis was verified by subsequent surgical operation, and also a few cases of achylia gastrica and achlorhydria, some associated with diarrhoea, and some not.

⁶ La Semaine méd., 1909, II, 13.

⁷ Les Procédés d'Examen des Fonctions du Pancreas, Thèse, Paris, 1910.

⁸ Berl. klin. Wehnschr., 1909, XLVI, 1406.

⁹ Zentralbl. f. inn. Med., 1913, XXXIV, 1.

¹⁰ Münch. med. Wehnschr., 1913, LX, 2158.

¹¹ Am. J. Med. Sc., 1913, CXLV, 393.

Carcinoma of the Pancreas.—Five cases of carcinoma of the pancreas were studied, three verified by operation and each very extensive, the head of the pancreas being especially involved; a fourth presented the typical picture of the disease, fatty stools of the most marked type, absence of trypsin in the stool (as all the other cases of carcinoma showed, the method employed being the Fuld casein method), negative results with the Schmidt nuclei test and positive Cammidge reaction, but this patient was not operated upon, and at her death an autopsy could not be obtained, while the fifth case is still alive, and presents a typical picture of the disease. All the cases were advanced cases of the disease—in four jaundice had been present for a long time, in one there was no jaundice. In one case gall-stones were also found.

In all five cases the first tube in our series showed no evidence of starch digestion, and we, therefore, employed supplementary tubes with lower dilutions, 2 cc., 3 cc., 4 cc. and 5 cc. of diluted feces being put in each of these tubes respectively, and 2 cc. of the 1 per cent starch solution added to each. In each case there was still no evidence of starch digestion in the tube of least dilution (5 cc. of stool, 2 cc. of 1 per cent starch) corresponding to 1200 of our units (or 12 of the starch gramme units employed by some others), and we did not study lower dilutions as we believe that the limit of error had been reached. Thus in each of these cases we can say that there is practically no diastase in the stool. Wynhausen showed a lessening in one case of tumor of the pancreas; Enriquez, Ambard and Binet found no diastase in the stool in 2 cases of cancer of the head of the pancreas, verified by autopsy, and Durand found no diastase in one case of probable carcinoma of the pancreas.

According to modern views, based on the experiments of Wynhausen,¹² Wohlgemuth¹³ and others, almost all the stool diastase comes from the pancreas, and its absence from the stool is, therefore, very suggestive of some marked disturbance of that organ, probably organic, such as cancer, possibly, although improbably, functional. Complete closure of the pancreatic duct was associated with very weak diastase reaction in the stool as shown in one case by E. Müller,¹⁴ and with no fecal diastase in one case by Durand, and if this obstruction is recent, the urinary diastase shows a marked increase according to Wohlgemuth.

Chronic Pancreatitis.—We have made quantitative estimations of the stool diastase in 6 cases of chronic pancreatitis, all verified by operation, a small, hard, definitely diseased organ being found in each case; 3 of the cases showed jaundice of long duration and in these the common duct passed through the head of the pancreas; 3 were not jaundiced, and at operation these cases showed extensive adhesions in a large extent of the right side of the abdominal cavity—involving appendix, cecum, ascending colon, and gall-bladder, and associated with marked constipation; in only one of the 6 cases was there a complete absence of free hydrochloric acid in the gastric con-

tents; one of the cases showed an alimentary glycosuria; one of the cases had gall-stones.

The diastase in the stool in these cases showed 12,000; 8000; 7500; 8000; 7500 and 3300 of our units respectively—in other words, diastase was present, but with marked diminution in all cases, the highest reading being only $\frac{1}{5}$ of the low-normal. Ehrman¹⁵ reported a case of chronic pancreatitis with hardening of the head of the organ, with much diminished diastase in the stool, and Durand reports 3 similar cases.

It would seem, therefore, that in cases of chronic pancreatitis diastase is present in the stool, but in markedly diminished amount. There was practically no difference in the cases with and those without jaundice, thus calling attention to the fact that while jaundice of short duration probably increases the amount of diastase by the activating influence of the bile, as shown by Wohlgemuth,¹⁶ nevertheless, the longer action of the bile upon the pancreas is to gradually lessen its functioning activity, as also suggested by certain experiments of ours¹⁷ upon dogs.

Achylia Gastrica and Achlorhydria.—We have studied a few cases of achylia gastrica and achlorhydria because of the physiological interest attached to such conditions. If, according to Starling, it is the action upon the duodenal mucous membrane of the free HCl, which alone calls forth the secretion of the pancreas by converting prosecretin into secretin, then in the cases of absence of free hydrochloric acid there should be a marked diminution of pancreatic secretion, unless there is a vicariously increased production in the other sources of the ferment. In the case of the diastase this is most improbable, as the minimal amount found in the bile and the very small amount in the secretion from Brunner's glands represent the only other available sources in the intestines, or in the lack of the usual mechanism, some other form of stimulation is called forth, and in this connection Pawlow's views that a nervous reflex plays a large part in stimulating the pancreas must be given more consideration.

In 7 cases of achylia gastrica a quantitative estimation of the stool diastase was made; 3 of these cases had persistent diarrhoea, the so-called gastrogenous diarrhoea; in each of the 7 there was no free and no combined HCl, and the total acid was 12 or less; in three of the cases tested no pepsin was found, the Edestin test being used. Of these 7 cases in one the stool contained 30,000 units, in three, 60,000 units, and in three, 120,000 or more—in other words, there was no diminution below normal in 6 of the 7 cases, while in one case there was only a slight diminution.

These findings are of interest, in the first place, because they show that in the absence of free hydrochloric acid some other method must be employed to call forth the pancreatic secretion, and, in the second place, the diarrhoea in some at least of these achylia cases is not due to an associated achylia pancreatica, as O. Gross has suggested, but is probably due to the associated enteritis. Whether the pancreas stimulation

¹² Loc. cit.

¹³ Berlin. klin. Wehnschr., 1910, XLVII, 1444.

¹⁴ Loc. cit.

¹⁵ Deutsche med. Wehnschr., 1909, XXXV, 879.

¹⁶ Loc. cit.

¹⁷ Johns Hopkins Hosp. Bull., 1912, XXIII, 263.

is of humoral or nervous origin in these cases, or whether both play a part it is difficult to say—the fact that peptone, salt, lipoids, lecithin, and fats can activate the pancreas must be remembered, and in some of these cases, at least, both modes of pancreatic stimulation have been demonstrated. Our results in this connection agree with those of Ehrman,¹⁸ who studied a similar group of cases by aspirating the stomach after the administration of the Volhard oil meal and testing the fluid obtained for trypsin by the Fuld casein method. His conclusions were that in achylia gastrica and gastric anacidity the function of the pancreas is not harmed but is sometimes even better than normal, and that, therefore, to stimulate the pancreas HCl is not necessary, in fact, is not the necessary activator of the pancreas as he has shown on dogs with pancreatic fistula. His method is to be regarded more as a qualitative than a quantitative one.

As to the etiology of the achylia in our series of cases, carcinoma could probably be excluded in all; in all but one—a young man—the patients were past middle age, and had either defective teeth or pyorrhœa alveolaris or both; in three of the cases a marked splanchnoptosis was present; in two a long alcoholic history, and in only one, a young man, was there a history of prolonged overwork and worry. No case showed that stool suggestive of pancreatic disease—stercorrhœa, and it has been our experience that this finding is extremely rare in achylia gastrica.

Our series of normal and pathological cases is a comparatively small one, but the results are very suggestive and warrant further study. In addition to continuing our studies along the lines mentioned in this paper, we are also investigating by this same method the diastase content of the stool in obstructive and catarrhal jaundice, in diabetes and in hyperchlorhydria and hypersecretion, and if the opportunity arises we shall make similar studies in diseases of the adrenal and thyroid glands, the close relationship between these glands and the pancreas being, of course, well-known.

Before concluding this article we wish to again call attention to the absolute necessity for the most rigorous technique in regard to the diastase test in the stool. As regards preliminary preparation we must remember that the stool obtained may represent one that has remained in the colon a considerable period of time unless especial precautions have been taken. For that reason in all cases we suggest a light supper the evening before, and a thorough emptying of the large bowel by means of a high enema, while if there has been any history of constipation we give in addition a saline laxative on the morning preceding the examination. By these means we believe we can practically always obtain a stool by our method which represents the response of the pancreas to the food and laxatives given, and also one in which the deleterious effect of the bacteria upon this ferment is reduced to a minimum. It might be well, however, to give with the milk some coloring matter, such as carmine, so that we might have visual evidence of this fact. Of course, the condition of the salts in the stool has also a distinct effect in activating or depressing the

diastatic action, but we do not believe that if our technique is followed out rigorously it is necessary to dialyze the stool and make our studies from the desiccated specimen.

In regard to the diet, we have insisted upon, first, a liquid food, milk, which does not stimulate salivary secretion, and, secondly, a measured amount because there is unquestionably a definite quantitative response on the part of the pancreas to the quantity as well as to the character of the food. The preservation of the specimen in a very cold place or on the ice and the immediate examination of it after the entire specimen has been obtained is absolutely essential because of the marked effect of temperature upon the action of the diastatic ferment, and also because if we allowed the specimen to remain long we are introducing two variable factors, one the influence of longer or shorter periods of time upon the diastatic ferment, the other the effect of varying bacterial flora upon this ferment.

We believe that the wide variation in figures obtained in certain of the investigations is dependent upon the lack of insistence upon certain of these points, and that if the technique is carried out as rigorously as outlined above the figures as to normal limits should be of real value. We have chosen the stool in preference to the duodenal contents obtained by aspiration in this group of cases because we believe thereby we can better measure the total output of the pancreas.

Conclusions.—From our study on diastase content of feces in normal and in certain pathological conditions the following conclusions seem warranted in being drawn:

1. The stool, if a rigorously exact method is carried out as to food, purgative employed, preservation of specimen, estimation of ferment, etc., furnishes a diastase content within definite limits. We cannot insist too strongly upon the procedure being *exactly* the same in all cases. The effect of waiting too long after the stool has been obtained before making the examination, the influence of variations in temperature in the place where it is kept, and of different laxatives and different foods is so great as to render results, obtained by methods in which insistence upon such a rigorous technique has not been made, of much less value.

2. Extensive carcinoma of the pancreas showed no diastase in the tube of lowest dilution in our method, and this absence of ferment should prove of great help in the diagnosis of this condition.

3. In chronic pancreatitis diastase was present in the stool, but in markedly diminished amounts.

4. In achylia gastrica the diastase content of the stool was practically normal in all the cases examined. This, in the first place, suggests that in the absence of hydrochloric acid some other method of pancreas activation is called into play, and, in the second place, that the diarrhœa met with in certain of these cases of achylia gastrica—the so-called gastrogenous diarrhœa—is not of pancreatic origin.

5. If all the controllable factors are standardized, the results obtained by the study of the diastase content of the stool should be of real value in the diagnosis of pancreatic diseases and in the study of functional disturbances of this gland.

¹⁸ Loc. cit.

THE PERIPHERAL ORIGIN OF SURGICAL SHOCK.

By FRANK C. MANN, M. D.

(From the Laboratory of Experimental Surgery of Indiana University.)

Despite the enormous amount of work which has been done on surgical shock, there is still among recent writers no general agreement as to the causes and nature of this condition. A critical review of the literature reveals an astounding amount of contradictory experimental data, and a great number of diverse conclusions based thereon. This condition of the subject was our reason for undertaking the present investigation. Our plan of attack may be summarized as follows:

(1) To determine definitely what is and what is not shock.

(2) To settle as nearly as possible, and one by one, the chief questions in dispute. These, so considered, are not of overwhelming difficulty. Most of them have already been worked out by the pathologists and physiologists. When necessary we have resorted to animal experimentation, taking especial care in each case to devise experiments the results of which can be readily verified.

(3) Either to correlate and harmonize the separate conclusions arrived at by the methods just described into a comprehensive theory of shock, or else to define as nearly as possible the limits of our present knowledge.

Definition.—The word “shock” is used in a very loose and vague way in medical literature. Some writers speak of “hemorrhagic shock,” “psychic shock,” “toxæmic shock,” etc. This use of the term makes it synonymous with injury. A study of the clinical reports of the patients supposed to have suffered or died from shock shows how frequently this word covers our ignorance of what is really the cause of a patient’s trouble, and also makes evident the necessity of excluding hysteria, cerebral injury, toxæmia, concealed hemorrhage, the effect of heat or cold, and many other conditions before the diagnosis of shock is justifiable. The use of the word shock is comparable to that of the word rheumatism. The latter formerly included every disease of the joints, and many other diseases besides, but has been restricted gradually to very narrow limits.

As Meltzer,¹ Porter,² and others have emphasized, we have only a clinical definition of shock. No lesions of any organ or organs the presence of which will account for all the phenomena of shock have ever been conclusively demonstrated. The signs of shock are thus given by Meltzer: “A state of general apathy, reduced sensibility, extreme motor weakness, great pallor, very rapid small pulse, thready soft arteries, irregular gasping respirations and subnormal temperature.” Meltzer insists that the presence of the circulatory phenomena is not absolutely necessary to the diagnosis. This definition is perhaps the best which can be given for this vague term, and with it we believe that most clinicians will be satisfied. It has the great merit of not involving any more or less questionable theory of etiology. Such a condition may arise in the course of various diseases, or of surgical operations, or may result from accidents or intoxications. The word shock is often used where accidental or operative trauma has had

nothing to do with producing the condition described. We have, however, for the sake of definiteness, limited our use of the word to conditions associated with trauma.

Historical Review.—The history of the development of present-day ideas of shock has been so carefully reviewed in recent years in several easily accessible articles (see 1, 3, 4, 5) that it is unnecessary for us to go into this phase of the subject in an exhaustive manner. We give the following brief historical review, not to evaluate or harmonize the various theories of shock at present in vogue, but to show the unsettled condition of the whole subject, and how this state of affairs has come about.

In very early times it was observed that patients who had been injured might fall into a depressed lethargic state in which death might occur. Such cases were noted in which autopsy revealed no lesion adequate to account for death. The word “shock” was probably first used in the early part of the eighteenth century to describe an occasional effect of gunshot wounds, for it was believed that the impact of a bullet caused a “commotion of the elements of the nervous system” which accounted for the symptoms observed. From this period to the present almost every writer on surgical subjects has discussed shock. The ideas of the older writers on shock were vague, though they foreshadowed nearly all the modern theories of this condition.

Thus Travers³ (1826) states that “shock is a species of functional concussion by which the influence of the brain over the organ of circulation is deranged or suspended.” And Savoy⁴ (1860) writes that “death from shock results from sudden and violent impressions in some portions of the nervous system acting upon the heart.” Thus writers have anticipated the modern theories of vaso-motor paralysis and cardiac failure.

Delcasse⁵ (1834) defined shock as “an arrest of innervation without which all organs pass into insensibility.” This is the old way of stating Meltzer’s inhibition theory.

Gross⁶ (1872) poetically describes shock as “a manifestation of a rude unhinging of the machinery of life.” Goltz¹⁰ (1872) is usually regarded as having made the first noteworthy experimental observation bearing upon the etiology of shock in his well-known “Klopfversuch.” This observation for a long time seemed to support the idea still held by many that vaso-motor failure is the cause of shock. Although this theory, in a form more or less vague, had been held for a long time, Crile¹¹ in this country and Mummery¹² in England have been mainly responsible for formulating it definitely and for removing it from the realm of possibilities to that of supposedly demonstrated scientific fact. It has been most vigorously opposed by Porter.¹³ The controversy between Crile and Porter is thus summarized by Meltzer:

According to Crile the failure of blood pressure is the primary and sole cause of all the symptoms of shock, and this failure has

as its cause solely the exhaustion of the vaso-motor center. The cardiac and respiratory failures and their phenomena are only secondary consequences or subsidiary factors to the primary cause, the exhaustion of the vaso-motor center"

The vaso-motor studies of W. T. Porter alone and with his pupils led him to results and views entirely antagonistic to those brought forward by Crile. In the first place, in disagreement with Crile, he states that in his numerous experiments he failed to find an instance in which stimulation of the afferent nerve caused a sufficient fall of blood pressure, except, of course, on stimulation of a depressor nerve. In his experiments crushing or electrical stimulation of the testis always gave a rise and not a fall of blood pressure. Continuous stimulation of the central ends of the sciatic, brachial or other afferent nerves for many hours gave uniformly the same rise of pressure as at the beginning. An analysis of 765 blood pressure records from stimulation of the sciatic and brachial (and depressor) nerves of rabbits, cats and dogs brought out the result that the "percentage change in blood pressure, which is the true index of the condition of the vaso-motor cells, increased as the blood pressure falls." Even in experiments where all the clinical signs of shock were present, the blood pressure very low, the temperature subnormal, the heart beat weak and often irregular, and the irritability of the nervous system apparently much reduced, stimulation of the depressor nerve lowered the blood pressure by 45 per cent. All these data, says Porter, are wholly opposed to the hypothesis that exhaustion of the vaso-motor center, brought on by over-stimulation, can be the cause of shock, but he is very emphatic in his assertion that the vaso-motor cells in shock are neither exhausted, depressed nor inhibited. Porter contradicts Crile's facts and disagrees with his exhaustion theory; but apparently he also disagrees with Howell's view, that inhibition of the vaso-motor and cardiac centers is at the bottom of the phenomena of shock.

The disturbance of pulse rate that is so often noted in shock has led some observers to look to a disturbance of heart action as a primary cause of shock. Thus Howell¹⁴ thinks that one of the causes of shock is inhibition of the cardio-inhibitory center. Boise¹⁵ states that the essential cause of shock is excessive sympathetic irritation manifested mainly by a tonic contraction of the heart and arteries. "Shock is therefore due to cardiac spasm; an incomplete ventricular relaxation, mainly of the right side." This reflex stimulation he supposes to pass through the accelerator nerves by way of the stellate ganglion.

Almost the exact antithesis to the vaso-motor failure theory is the theory of Malcolm.¹⁶ His view is that the arteries, more especially the peripheral arteries, are contracted during shock and that as a result of this the blood is "forced into the splanchnic area." This, he thinks, leads to important changes in the composition of the blood and tissues.

The idea that inhibition is a cause of shock is a very old one and is the basis of many theories. The terms vital depression, inhibition of innervation, inhibition of the vaso-motor center, inhibition of the cardio-inhibitory center (Howell), all testify to the wide prevalence of this thought. Meltzer¹ has formulated the inhibition theory in the broadest and most satisfactory manner. He presents as evidence for his conclusions some observations upon the cœcum of the rabbit. The movements of this organ can be observed in the intact animal through the abdominal wall. They cease when the skin of the abdomen is incised. He has shown that this

is due to a definite inhibitory reflex. He thinks that perhaps other functions can be inhibited in a similar manner. He deserves special credit for emphasizing the fact that low blood pressure and an accelerated pulse rate are not always present in shock.

Leonard Hill¹⁷ states that in his opinion shock is due to a depression of the sensory synapses, producing a decrease in tone of the central nervous system.

The most recent and at the same time the most radical departure from the other theories of shock is that of Henderson,¹⁸ who believes that shock may be caused by a loss of carbon dioxide by the tissues; the loss being brought about by excessive pulmonary ventilation or by exhalation of carbon dioxide from exposed viscera. He denies that vaso-motor failure is present in shock and claims that the development of shock may be prevented by safeguarding the body from loss of carbon dioxide.

Various other possibilities have been suggested as a cause of shock. Among these might be mentioned the hypothesis that it is a derangement of the thermogenic mechanism;¹⁹ that it is a condition of perverted metabolism due to trophic impulses;² that it is due to a pathological change in the chromaffin tissue.²⁰ Little or no evidence has been produced to support these hypotheses.

A great amount of work upon special phenomena of shock has been done, for example, upon the state of the arteries, the condition of the various vital centers, the specific gravity, gaseous and cellular content of the blood, etc. To much of this work we shall have occasion to refer later.

Method of Experimentation.—The experiments described in this article were performed upon animals which were under full surgical anesthesia. Ether was the anesthetic used. No animal was allowed to feel pain at any time, and all the animals were killed before they regained consciousness.

Scope of the Present Investigation.—We wish to emphasize here at the beginning that the scope of the present experiments includes the phenomena which occur in the anesthetized animal. Our results, while strictly comparable to what may be observed on human patients during operation, do not apply to cases of so-called "pure" shock which may be met with under the conditions of ordinary life. Shock of this kind may be due to much more complex causes than the type we have studied.

Original Investigation—the Standard of Shock.—We found it very difficult to determine when an animal had passed into a state of shock. In the protocols of some observers a markedly lowered blood pressure is taken as the sole indication of the presence of shock. Other workers note, in addition to the blood pressure, the pulse and respiration. It can be demonstrated all too easily that low blood pressure, rapid pulse and irregular respiration may be produced by the action of the anesthetic alone. It seems to have been thought sufficient to state: "after reducing the animal to a state of shock" without giving either the method of its production or any criteria by which it is possible to judge whether the animal really was or was not in a condition of shock. This lack of definite-

ness in regard to these fundamental matters makes many of the most extensive researches on shock of somewhat questionable value.

We have regarded no animal as being in a condition of shock unless the following signs were present:

1. Loss of sensibility as shown by the lack of necessity of administering an anesthetic when the eye reflex was present.
2. Pallor of the mucous membranes.
3. Small weak pulse.
4. Irregular, rapid, shallow or gasping respiration.
5. Markedly lowered blood pressure.

The fundamental importance of these criteria merits a discussion of them. When all the above signs are present, and when there has been no hemorrhage, we believe that it will be generally admitted that shock in the full clinical sense of the term is present.

We were impressed by the fact that in many cases an animal might show all the signs given above except a markedly lowered blood pressure. Many times we observed dogs which presented pallor of mucous membranes and impaired respiration, and which required but little anesthetic for several hours, but in which the blood pressure was but 20 to 40 mm. lower than at the beginning of the experiment. In order, however, to make our results absolutely beyond criticism we always continued our manipulations until the blood pressure was only one-third to one-fourth its original level before we regarded the animal as in shock.

The Production of Shock.—Our first endeavor was to find the quickest and most certain method of producing shock. We were exceedingly careful to avoid even the slightest hemorrhage. In a special series of twelve dogs experimented upon for this special purpose, and in a large number of others on which the observation was incidentally made, we attempted to produce shock by traumatization without opening the abdomen. Despite the most persevering efforts, we could reduce only two of these animals to a condition which was thought to be shock. In all the others the blood pressure was just as high or only a few millimeters lower than at the beginning, and just as much anesthetic had to be administered to keep the eye reflex inactive as is necessary in any experiment of the same length of time (3 to 5 hours).

It was also impossible to produce shock in an anesthetized animal by traumatization of the great nerve trunks. These results corroborate Porter's¹³ conclusions. Long-continued stimulation, either electrical or mechanical, of large numbers of afferent fibers did not produce the condition. Intermittent stretching of a mixed nerve like the sciatic usually produced fluctuation in blood pressure, but intermittent and simultaneous stretching of both sciatics, both anterior crurals and both brachial plexuses for a period of four hours did not produce the signs of shock. It is true that blood pressure, respiration and pulse were affected by these manipulations, but in no case were they markedly affected, providing, of course, that there was no hemorrhage. The blood pressure fluctuated slightly, rarely over 10 mm.; in some cases a slight fall occurred. The greatest fluctuation occurred under light etheri-

zation. During deep anesthesia the most severe traumatization did not affect blood pressure, respiration or pulse.

In the two animals in which shock was thought to have developed, autopsy showed that very large concealed hemorrhages had occurred. These findings indicate that great care must be used to exclude hemorrhage before making a diagnosis of shock.

Our results in this special series of experiments and in many other experiments in which we have had occasion to observe the effects of trauma upon the anesthetized animal are so consistent and invariable that we do not hesitate to state that it is impossible to reduce a dog to a state of shock in 4 to 5 hours by traumatization alone, without opening the abdomen, without inducing hemorrhage or without trauma to the medullary centers. These results corroborate the findings of Hill²¹ and also Janeway.²²

The Production of Shock by the Use of Excessive Heat or Cold.—Heat: Investigators who have used heat to produce shock have endeavored to stimulate as many sensory nerve endings as possible. There are, however, many factors other than the stimulation of the sensory fibers involved in such experiments: Perhaps the most important of these is the increase in the temperature of the animal. Since the dog eliminates heat chiefly by way of the lungs its respiration is greatly increased in rate and depth. That this hyperpnea is due mainly to the increased temperature may readily be shown by applying cold to the parts of the animal which are not subjected to the heat. If this be done the hyperpnea will not occur. Furthermore we shall cite evidence to show that heating the blood causes important changes in the various tissues of the body.

We have found that heat applied to the feet or large body surfaces of the etherized dog does not produce any permanent effect upon its blood pressure, although slight fluctuation of the same may occur during application. In order to control the conditions of the experiment better we devised a method of heating only the blood of the animal. This was accomplished in three different ways:

First: Both carotid arteries for as long a distance as possible were carefully freed from the neighboring structures which were protected from heat by gauze saturated with salt solution. Warm water was then circulated through the coil which encircled each carotid.

Second: The hind leg of the animal was completely severed from its body except for the femur and femoral vessels. These vessels were dissected free for some distance and gauze saturated with salt solution at 60° C. was placed around them.

Third: By injecting hot water into the rectum.

Heat applied in any of these ways will reduce a dog in from 2 to 3 hours to a condition in which all the signs of shock are present. If light anesthesia be used hyperpnea will develop, but if the dog be deeply etherized the pulmonary ventilation is decreased. We have observed no effect of the breathing in either case on the time at which shock developed. In the experiment on the dog with the partially severed leg this limb at autopsy was found to be swollen to several times

its normal size. On incising it clear fluid poured freely from the cuts. In all the animals the blood at autopsy was found to be dark and thick and all the veins, both splanchnic and peripheral, were dilated.

The condition produced in these experiments fulfilled all the requirements of the clinical definition of shock. Death seemed to result from primary cardiac failure. We can state most emphatically that the condition did not result from traumatic stimuli, or loss of carbon dioxide, but was wholly due to over-heating of the blood. We positively demonstrated that the vaso-motor center was active, because it constantly responded to the tests which we shall discuss later.

The effect of excessive cold was observed upon an animal which was subjected to a continuous rectal injection of ice water. In an hour and a half the animal was reduced to a condition resembling shock. The only noticeable difference between the condition of the animal in this experiment and that of those which had been subjected to heat was the character of the pulse. The rate of the heart beat was greatly decreased and the amplitude of the beats increased. Section of the vagi only slightly modified the cardiac action. The animal died from primary cardiac failure.

The Production of Shock by Forced Ventilation of the Lungs.—We attempted to produce shock by Henderson's²⁸ method of forced lung ventilation. In a limited number of experiments of this character we were able to produce the condition in only one case. Our trouble was probably the same as Henderson records in regard to his first experiments—an inefficient pump. But we are quite certain that the artificial ventilation was greater than it would be possible for the animals themselves to have produced by the greatest possible forced respiratory movements. In the one case in which the signs of shock did appear autopsy revealed the fact that both lungs, with the exception of a small part of the upper left lobe, were consolidated. We could not determine whether this condition had existed before the beginning of the experiment, but as the dog was apparently a perfectly healthy animal, it is extremely probable that its lungs were normal.

The Production of Shock by Opening the Abdomen and Exposing the Viscera.—Our next method was to open the abdomen and expose and traumatize the viscera. This in every instance produced shock. Sometimes the condition came on quite rapidly; in other instances the process was delayed. Upon opening the abdomen the blood pressure usually fell, due to lowered intra-abdominal pressure. While the viscera were being exposed the blood pressure showed marked fluctuations, due to the mechanical manipulations. If the intestines were squeezed the pressure might temporarily become greater than normal, because of the better filling of the right side of the heart. But gradually blood pressure fell and usually within an hour shock was present. In many cases it was not necessary to administer ether after the abdomen was opened, even when the experiment extended over a period of several hours.

In reviewing the protocols of various observers it is interesting to note their use of visceral traumatization to produce

shock. It is surprising how few experiments are on record in which, if the method of producing shock is stated at all, this was not the means employed. The observer may begin an experiment by crushing a foot or burning a part, and may obtain some fluctuation in blood pressure by such means, but sooner or later, as if discouraged by the progress made, he invariably adds, "and the intestines were manipulated." The protocols are few which do not record directly or indirectly a complicating hemorrhage or a section of the abdomen.

In all our experiments, unless otherwise stated, shock was produced by exposing and traumatizing the abdominal viscera of an etherized animal. The condition was never called shock unless the clinical signs as previously stated were present, except in special experiments, *e. g.*, in the use of curare, section of the cord, etc., which made it impossible to note some of the signs.

The Condition of Various Tissues and Systems in Shock.—An endeavor has been made to study individually each system which might be affected in shock, the attempt being to determine what part it played in the production of shock, and how it was affected by the resulting condition.

The Vaso-Motor Mechanism in Shock.—The Vaso-Motor Center: Our work corroborates Porter's²⁹ conclusions in regard to the condition of the vaso-motor center in shock. Stimulation of mixed nerves produced a marked rise of blood pressure, even in extreme degrees of shock, and stimulation of the depressor nerve produced a comparable fall in the same condition. We were able to corroborate Seelig and Lyon's²³ results in regard to the effect upon the blood pressure of stimulating the central end of the vagus. In every case this yielded a rise of blood pressure in shock. In some instances the rise was actually greater in the shocked animal than in the normal one.

The reaction of the center to the concentrated hydrogen ion content of the blood is as marked after the production of shock as before. The production of a wide pneumothorax in a shocked animal gives a blood pressure tracing not influenced by the respiratory movements. Under these conditions an asphyxial rise in the blood pressure takes place. In some cases the pressure of an animal in marked shock was more than doubled; in other instances but a moderate, and rarely but a slight rise occurred. The same result was obtained if the animal were made to inhale high percentages of carbon dioxide. The injection of lactic acid does not produce a constant result even in the normal animal. However, we have records which show a marked increase in blood pressure in the shocked animal produced by this supposedly normal chemical stimulant. An increase of intra-cranial pressure produced the same relative increase of blood pressure in the shocked animal as in the normal one.

The Condition of the Arteries in Shock.—The Peripheral Arteries: The pallor which occurs in shock might be due to one of two causes: (1) The constriction of the peripheral vessels, which prevents a flow of the blood to the skin; or (2) to a dilatation of the splanchnic vessels, which causes the blood to be drained out of the skin. Seelig and Lyon²⁴ have

recently investigated the condition of the peripheral arteries in shock and have concluded that these vessels are constricted. Bartlett,²⁵ who has investigated the same question, reaches an exactly contrary conclusion.

Neither of the methods used by these investigators gave conclusive results in our hands. For this reason we employed older and simpler physiological methods. During the production of shock, peripheral venous pressure, as taken from the femoral vein, decreases. This is usually very marked and may take place before blood pressure has greatly decreased. If the sciatic is cut in the shocked animal there is an immediate and decided increase in the pressure of the femoral vein. This is evidence that the arteries of the limb are constricted during the production of shock and that there is considerable vaso-motor tone, even when the blood pressure is very low.

The tongue of the dog is an organ which is liberally supplied with vaso-motor fibers. Fortunately these run in separate nerve trunks. The major part of the dilators pass through the lingual nerve,²⁶ while the constrictors are carried in the hypoglossus. This furnishes an ideal arrangement for the study of this particular phenomenon. If one hypoglossal nerve is stimulated in a curarized dog the tongue becomes slightly paler on the side innervated by this nerve; if the lingual nerve is stimulated the tongue becomes very red and the veins stand out very prominently upon the corresponding side. If the animal is reduced to shock the phenomenon, upon stimulating the lingual, is even more marked. The reddened muscles and bulging veins of the corresponding side contrast strikingly with the pallor of the opposite side of the tongue and the mucous membrane of the oral cavity. The vessels of the tongue are evidently in tone which is decreased by the stimulation of the dilator fibers. This tone might be due to vaso-constrictor impulses from the vaso-motor center or the arterial muscles themselves. That at least a part of this tone is due to the former cause is proved by the gradual but quite noticeable dilatation which occurs after section of the hypoglossal nerve which contains the vaso-constrictor fibers. In animals which normally have enlarged vessels of the tongue this result can be better observed if a slight asphyxia is produced in the shocked animal. Tracings of the volume of the tongue of a dog in shock show that it is decidedly increased upon stimulation of the lingual nerves. This experiment proves that the arteries of the tongue are still subject to considerable vaso-constriction in shock.

A large number of the vaso-constrictor fibers of the rabbit's ear run in the cervical sympathetic nerve²⁷ which forms a separate trunk in that animal. The blood vessels of the ear of the albino rabbit show vaso-motor changes quite distinctly. As shock develops these blood vessels become constricted until they are small, more or less faint, lines. That this decrease in caliber is not a passive condition is shown by the fact that lowering of the ear below the level of the splanchnic area does not produce a congestion of these vessels, while section of the cervical sympathetic nerve produces a noticeable dila-

tation of them. They are, therefore, under vaso-motor tone in shock.

The unpigmented paw of a kitten or puppy is well suited for the study of vascular changes in the limbs. The vaso-motor fibers of the paw run in the sciatic nerve.²⁸ If the sciatic on the one side is cut in the normal animal the corresponding paw assumes a brighter tint than its fellow. In the beginning of shock the difference becomes more marked, because the paw with the intact nerve becomes paler. It is only when the blood pressure is very low in marked shock that the paws look alike. Even then a difference can be observed by lowering both paws below the level of the splanchnic area, when the paw with the intact nerve becomes paler. If the sciatic of the intact leg be now severed a faint but distinct flush appears on this paw. This experiment shows that the blood vessels of the paw are under vaso-motor tone in shock.

The Untraumatized Visceral Arteries in Shock.—The arteries of the kidneys were taken as the most accessible of the untraumatized visceral arteries to study. The vaso-motor changes were recorded by means of an oncometer. This can be applied through a lumbar incision without entering the abdominal cavity and without disturbing blood pressure. Tracings of the volume of the kidneys were taken before, during and after the production of shock.

During the production of shock there was usually an immediate kidney shrinkage, although this did not invariably occur, for at times an initial expansion occurred, while in other instances the volume of the kidney passively followed the changes in the general blood pressure.

Roy and Bradford²⁹ have shown that stimulation of the central end of the sciatic nerve produces a decrease in kidney volume, while it increases the general blood pressure. Our results show that when the blood pressure is very high in the normal animal, stimulation of the sciatic nerve does not always produce a shrinkage of the kidney. A slight expansion may occur, but this increase in kidney volume is always so small as to show that some vaso-constriction is occurring, although not quite enough to offset the rise in general blood pressure.

Stimulation of the sciatic nerve in moderate degrees of shock *always* produces a marked decrease in kidney volume, although the rise in general blood pressure might be as great as in the normal animal. In some cases this decrease in kidney volume following stimulation of the sciatic could be obtained with a blood pressure of only 20 mm. Additional evidence of the vaso-constrictor tone of the renal vessels was secured by recording the increase in volume of the kidney following cauterization of the renal vessels with carbolic acid, which destroys the vaso-constrictor fibers.

It is evident from these experiments that the tone of the vaso-constrictor mechanism of the kidney is increased in a moderate degree of shock, and that it is not entirely absent even when the blood pressure is very low.

The Character and Flow of the Lymph in Shock.—This was investigated by observing the rate of flow from the

thoracic duct. A canula was inserted into the duct extrapleurally without producing any disturbance in blood pressure or respiration. The rate of flow was determined by counting the drops or accurately measuring the amount of flow per unit of time. Care was taken during the reading to exclude the effect of irregular respiration or manipulation of the intestines. A normal rate was always determined before shock was produced. The following results were obtained: At the onset of shock the lymph flow through the thoracic duct was slightly increased. As shock developed it might decrease slightly below normal. In character the lymph changed from a color more or less milky to a pale reddish color. Microscopic examination showed many red cells present. The coagulation time was markedly decreased, so much, in fact, that toward the end of an experiment it was almost impossible to maintain a flow from the canula. At this time the lymph resembled an exudate.

The Cardio-Inhibitory Center in Shock.—This center is thought by some investigators to be inhibited in shock, while others claim that it loses tone. The following facts throw light upon this point:

1. An animal which has had the vagi cut does not seem to develop shock any more quickly than one in which they are intact.

2. It is well known that if one vagus is severed while the other is left intact and the central end of the divided one stimulated, a rise in blood pressure occurs. However, by carefully graduating the current in some animals a reflex inhibition of the heart can be produced. In each dog in which it was possible to obtain this reflex it remained positive, even in the most extreme degrees of shock. That this inhibition of the heart was a definite reflex, involving the inhibitory center, was shown by section of the intact vagus in the deeply shocked animal; after this it could not be again obtained.

3. In the normal adrenalin curve, after the initial rise in blood pressure, inhibitory beats occur which have been proved to be due chiefly to a reflex involving the inhibitory center, although increased filling of the heart may be a factor. In the tracing obtained by the injection of adrenalin in the shocked animal the same characteristic beats occur, after blood pressure has slightly increased. We observed their disappearance in shock after section of the vagi and an increase of blood pressure to six times the height present before the drug was injected.

4. An increase in intra-cranial pressure produces characteristic inhibitory beats of the heart, due in all probability to bulbar anemia. These occur when the intra-cranial pressure is increased in the shocked animal, and cease when the vagi are cut. The blood pressure then increases enormously, for the vaso-motor center also reacts to the increased intra-cranial pressure.

These experiments would seem to prove conclusively that the cardiac inhibitory mechanism is intact, even in the deeply shocked animal.

The Heart in Shock.—In all the experiments in which the animal was allowed to die from uncomplicated shock the heart was beating, although sometimes quite feebly, when respiration had ceased and blood pressure was practically zero. In many cases, upon opening the thorax when all signs of life had disappeared, the heart was observed to be contracting still. In the production of shock the pulse usually, but not invariably, increased in rate. The individual beats always became weaker, as measured by palpation and the manometric tracing, but the cardiac function remained until the very last.

Seelig and Lyon²⁴ have shown that typical shock can be produced after evulsion of the stellate ganglion. This certainly removes almost entirely the possibility of the heart being affected through the sympathetic system.

That the heart is capable of performing its function efficiently in shock, if only enough blood is returned to it, was pointed out by Hill.³⁰ He increased the venous return to the heart by visceral compression and noted that the heart was able to handle the increased amount of blood effectually. We have been able to corroborate Hill's results.

A more severe test of the efficiency of the heart in shock is afforded by the injection of large doses of adrenalin in the shocked animal after section of the vagi. This produces an enormous rise of blood pressure, often increasing the pressure to a level six times higher than that in shock. In every instance in which this was done the heart was able to pump against the enormous pressure effectually and in no instance was there an indication of cardiac failure. A similar test was made by increasing the intra-cranial pressure of a shocked animal in which the vagi had been cut. The vaso-motor center was stimulated and the blood pressure increased enormously, but although this was maintained for several minutes, the heart remained competent to perform its function.

In view of these facts it is impossible to believe that the heart is the primary factor in the production of shock. These experiments prove that the heart is as efficient a pump in shock as in any other condition in which it has been subjected to a poor blood supply during a long period.

The Respiratory Mechanism in Shock.—As shock develops, respiration becomes more shallow and may increase in rate, but quite often decreases. The most characteristic respiratory phenomenon of shock is the intermittent gasping type of respiration. All our tracings obtained from animals which died of uncomplicated shock show that the respiration failed before the circulation. However, the respiratory center of a shocked animal responds quite actively to afferent stimulation, to rebreathing, to inhalation of carbon dioxide and to the injection of lactic acid. Stimulation of the vagus produces the usual inhibition of respiration in the shocked animal.

These facts show that the respiratory mechanism is not primarily at fault in the production of shock, but that it is probably the most seriously damaged and the most easily injured of the medullary centers by the resulting condition.

The Study of the Mesenteric Circulation in Shock.—In many experiments a microscopical study of the circulation of

the mesentery and omentum was made. The phenomena observed were those described by the pathologists in the classical descriptions of acute inflammation. These are: Dilatation of arteries and veins; congestion and slowing of the venous flow, which later results in a more or less noticeable stasis; margination and later emigration of the leucocytes; late in the condition rupture of many of the small vessels and escape of cellular elements into the tissue spaces or to the surface.

Histological sections of the omentum, mesentery and intestines of the normal and shocked animal were made and compared. These showed all the above phenomena in a static form and emphasized many of the facts which will be discussed later.

The Condition of the Blood in Shock.—Specific Gravity: There has been considerable controversy in regard to the specific gravity of the blood in shock. The preponderance of the evidence is in favor of an increase of specific gravity in this condition. We observed that if the blood were taken from the peripheral vessels it showed but a slight increase in its specific gravity, but if taken from the splanchnic vessels it showed a marked increase.

The Blood Corpuscles in Shock.—Crile,³¹ in a series of four experiments upon shocked dogs and dogs suffering from hemorrhage, comes to the following conclusions: In shock the red cells are increased while the white cells are decreased; in hemorrhage red cells are decreased while white cells are increased.

The condition of the blood in hemorrhage need not be discussed or investigated here, especially as this has been done so completely by many observers. In the series of experiments in which blood counts were made before and after the production of shock it was found that there was an enormous decrease of white cells in the shocked animal, while the red cells were slightly, if at all, increased.

The Production of Shock by Intra-Abdominal Traumatization Without Free Exposure of the Viscera to the Air.—In some experiments an incision into the abdomen just large enough to admit the hand was made. Through this a gloved hand was passed and the abdominal wall clamped snugly around the wrist. Intra-abdominal traumatization for a period of five minutes would lower blood pressure considerably, but if the traumatization were now stopped the pressure would soon return almost to normal. However, if the traumatization were continued for a much longer time the animal would develop the signs of shock. That this was not due to an exhalation of carbon dioxide was proved by passing a stream of a high percentage of this gas directly into the abdominal cavity. If the gas were admitted slowly so as not to increase the intra-abdominal pressure it did not delay the onset of shock.

Production of Shock After Section of the Cord.—Section of the cord in an animal in the horizontal position in the lower cervical or upper dorsal region produces an enormous fall of blood pressure, due to section of the vaso-constrictor fibers. That such an animal is not in a condition of surgical

shock can be shown by withdrawing the anesthetic, when the animal will regain consciousness and respond to stimuli applied around the head. Upon opening the abdomen of an animal in this condition the vessels of the splanchnic area are seen to be dilated and the viscera congested. But the exposure of the viscera produces a marked and immediate increase in the congestion in the same manner as in an animal which has not been subjected to section of the cord. The fall of blood pressure following section of the cord is not any greater than the decrease which follows immediately upon section of the abdomen and exposure of the viscera. Evidently typical shock can be produced after section of the cord.

Vaso-motor reflexes are not very easy to obtain or very marked in an animal with the cord severed. However, stimulation of the sciatic does produce a slight rise in blood pressure. A proportionate rise occurs even when blood pressure is very low, due to abdominal traumatization. A slight asphyxial rise of blood pressure occurs in a dog with the cord sectioned. A proportionate rise occurs when shock has developed.

The Effect of Hemorrhage Upon the Production of Shock.—During the course of some experiments accidental hemorrhages occurred. It was noted that shock developed very quickly in these cases. This observation agrees with the reports of a large number of clinicians. In order to study this condition more completely a series of experiments were performed in which the animal was subjected to varying degrees of arterial or venous hemorrhage and the same tests applied as in the experiments upon the shocked animal.

The most noticeable effect of a slight hemorrhage upon an anesthetized animal is the resulting depression of sensation. A dog of ten pounds weight could be subjected to a slow venous hemorrhage of 50 to 75 cc. without producing a fall in blood pressure of over 15 mm. But the loss of sensibility was such that in most cases only a very little, if any, anesthetic was necessary, even in long-continued experiments. If the bleeding were done from an artery of large size, as the femoral, blood pressure fell quickly during the hemorrhage, but if the loss of blood were slight, vaso-motor compensation would restore the pressure almost to normal. As the amount of blood lost was increased the power of vaso-motor compensation decreased until blood pressure remained very low. Furthermore, we found that the animals which had been bled responded to the same tests for the activity of the various centers in the same manner as the animals which had been reduced to shock. The condition of an animal after hemorrhage could not be differentiated from the condition of shock, except perhaps by a leucocyte count.

Summary and Conclusions.—The data we have presented justify the following conclusions:

1. It is impossible to reduce the anesthetized animal to a state of shock by any degree of sensory stimulation, provided all hemorrhage is prevented and its abdomen is not opened.
2. We have been unable to show that acapnia is a primary factor in the production of shock.
3. Shock is not due to disturbance of the respiration, but

the respiratory center is more quickly injured than any other vital center by shock.

4. The vaso-motor center is not depressed nor fatigued in shock. It is the most resistant of all the vital centers. The peripheral and untraumatized visceral arteries are constricted in shock.

5. Shock is not due to primary failure of the heart nor to involvement of the cardio-inhibitory or cardio-accelerator mechanism.

6. It is possible to produce the signs of shock by the use of excessive heat or cold.

7. The easiest and most certain method of producing shock is by exposure and traumatization of the abdominal viscera. This, judging from the literature, has been the method used by nearly all investigators of shock.

8. Shock produced by exposure and trauma of the abdominal viscera is not due alone to a paralysis of the vaso-motor mechanism of the splanchnic area. This has been shown by two crucial experiments. (1) Section of the cord or splanchnic nerves does not produce shock. (2) When all the abdominal and thoracic organs are taken from the animal (Carrel) this "visceral organism" can still be kept alive for many hours and it can digest food, excrete urine, etc.²² Therefore, some other cause than vaso-motor paralysis or inhibition is involved.

9. The cause of shock is the tremendous loss of red cells and fluid from the blood, due to the reaction of the great delicate vascular splanchnic area to irritation—an acute inflammation of the peritoneum, due to trauma and exposure to the air and changes of temperature. The great amount of this loss is apparent when it is taken into consideration that the peritoneum has an extent as great as the entire cutaneous surface of the body. The factors involved in this reaction to irritation are the same as those involved in any other local inflammatory process, and certainly do not involve the nervous system to any greater extent. The profound general effect is due to the actual loss of red cells and fluid from the circulating blood through stasis, diapedesis, exudate, endothelial changes, etc. It is to be noted that some of the classical descriptions of inflammation were made from observations on the exposed omentum and mesentery.²³ In the course of operations in which the abdomen has not been opened, a loss of fluid and cells from the blood occurs. But the loss is, except when great areas of subcutaneous tissue have been exposed, comparatively unimportant.

10. Certain accessory factors which help to produce the condition of shock should be mentioned. These are muscular relaxation, decrease in intra-abdominal pressure and impaired respirations, all of which tend to decrease the amount of blood returned to the heart. The effect of chilling and the use of hot applications should be considered.

11. Degenerative changes in the cells of the central nervous system are the result and not the cause of shock. Dolley²⁴ states that identical changes in the nerve cells are produced by hemorrhage and shock.

12. General anesthesia of moderate depth prevents painful

impulses from affecting the nerve cells of the central nervous system. Nerve blocking under such conditions is useless, so far as the prevention of shock is concerned.

13. A relatively slight decrease in blood supply may be sufficient to depress markedly the cells of the cerebral cortex. Care should, therefore, be taken to exclude this factor before ascribing such depression to inhibition.

14. The use of the word "shock" should be avoided, and instead an accurate and detailed description of the patient's condition should be given. If the term be used at all it should be applied to the condition in which, without any grossly discernable hemorrhage having occurred, the amount of circulatory fluid is greatly diminished on account of stagnation of the blood in the smaller veins and capillaries or by exudation of the fluid and cellular elements of the blood from the same.

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THE NORMAL DIASTASE-CONTENT OF THE URINE.

By THOMAS R. BROWN, M. D.,

AND

C. WHARTON SMITH, JR.

(From the Chemical Laboratory of the Medical Clinic.)

We have studied, in a series of cases, the amount of diastatic ferment present in the urine of normal adults in the hope, in the first place, that by establishing a normal the quantitative estimation of this ferment in the urine might be of value in the diagnosis of pancreatic disease, and, in the second place, to furnish criteria of some value in estimating the importance of this procedure as a test of renal function, since Wohlgemuth suggested this as a satisfactory method of estimating the secretory activity of the kidney, and Rowntree reported later a number of cases in this connection; as we shall see, probably its greatest value is as a test of renal function. The individuals in our series were normal men and women, with no demonstrable lesions of the kidneys or digestive apparatus, living on a mixed dietary.

In studying the urine we used a slight modification of the method first described by Wohlgemuth in the "Biochemische Zeitschrift," based on the conversion by diastase of soluble starch (Kahlbaum) into, successively, erythro-dextrin, achroo-dextrin, iso-maltose, and maltose, the limit being determined by that tube in which the addition of an iodine solution produces no blue coloration, *i. e.*, when all the soluble starch has been converted into lower products.

In determining the quantity of diastase in the urine, the twenty-four-hour specimen was carefully collected, kept under toluol in the ice-box, or in a cool place. This was diluted with distilled water to 3000 cc., and decreasing amounts of this diluted urine were added to a series of tubes.

In our first group of cases we used the method of geometrical progression—2 cc. in the first tube, 1 cc. in the second, ½ cc. in the third, ¼ cc. in the fourth, ⅛ cc. in the fifth, etc., but as the variation between contiguous tubes was too great by this method, we later, in our much larger series of cases, used the method of mathematical progression—1.8 cc. in the first tube, 1.6 in the second, 1.4 in the third, 1.2 in the fourth, 1 in the fifth, 0.8 in the sixth, 0.6 in the seventh, 0.4 in the eighth, 0.2 in the ninth, 0.1 in the tenth, 0.05 in the eleventh, and 0.025 in the twelfth, the last 3 tubes being, as seen, in geometrical progression.

Each tube was filled with distilled water to 2 cc., 2 cc. of a 0.1 per cent solution of soluble starch added to each tube, incubated for half an hour in the water bath at 38° C., rapidly cooled off at the end of that time by nearly filling the tubes with cool water, and by holding the tubes under the cool tap and then quickly tested by the addition of a few drops of 1/50 normal iodine solution, the limit being the tube just before the first tube in which blue is seen, this limit-tube showing the brown color which erythro-dextrin gives with iodine.

In the 10 cases studied by the former method the variations were comparatively small and in all cases more than 1000 units, the unit chosen being one cubic centimeter of 1 per cent soluble starch solution completely converted into lower products in one-half an hour in the water bath at 38° C.

As the variations between the contiguous tubes seem too great by this method the findings by the second method are of more value in furnishing exact figures (see Table I). Of

TABLE I.

Case	Urine		Limit-tube.
	Amount in 24 hours.		
1.....	1000 cc.		10 + 11 —
“ 2.....	1125 “		10 + 11 —
“ 3.....	750 “		8 + 9 —
“ 4.....	1000 “		10 + 11 —
“ 5.....	1820 ”		10 + 11 —
“ 6.....	1730 “		10 + 11 —
“ 7.....	500 “		8 + 9 —
“ 8.....	1520 “		10 + 11 —
“ 9.....	1460 “		9 + 10 —
“ 10.....	1070 “		9 + 10 —
“ 11.....	380 “		11 + 12 —
“ 12.....	370 “		9 + 10 —
“ 13.....	1450 “		11 + 12 —
“ 14.....	620 “		9 + 10 —
“ 15.....	320 “		8 + 9 —
“ 16.....	1900 “		11 + 12 —
“ 17.....	1250 “		10 + 11 —
“ 18.....	1440 “		9 + 10 —

the 18 cases in this series in 3 the limit was tube 8 (1500 units), in 5 tube 9 (3000 units) in 7 tube 10 (6000 units), and in 3 tube 11 (12,000 units).

While the variations are considerable, as one would expect from differences in the diet, as some foods are more stimulating to pancreatic and salivary secretion than others, and as the diastase is widely distributed in the body (being furnished as a digestive ferment by the salivary glands, pancreas, and, to a very slight extent, by Brunner's glands, and being present as an autolytic ferment in the liver, muscles, blood, in fact, in practically all the organs and tissues of the body), yet it would seem that the diastase content of the urine falls within definite, if rather wide, limits, and any figures smaller than the low normal found (tube 8, in our second method corresponding to 1500 units) would speak either for a less amount of circulating diastase or diminished renal permeability due to changes in the kidneys.

As the diluted urine was in some cases slightly acid, in other cases neutral, in others slightly alkaline, we studied in a new group of cases the effect of this variation in reaction upon the activity of the ferment (see Table II). We found that while a slightly acid medicine activated slightly the action

TABLE II.

Reaction.		Urine Amount in 24 hours.	Limit-tube.
Case 1.....	Acid	1460 cc.	10 + 11 —
	Alkaline	1460 "	9 + 10 —
" 2.....	Ac.	1550 "	10 + 11 —
	Alk.	1550 "	10 + 11 —
" 3.....	Ac.	720 "	10 + 11 —
	Alk.	720 "	9 + 10 —
" 4.....	Neutral	1220 "	9 + 10 —
	Ac.	1220 "	9 + 10 —
	Alk.	1220 "	9 + 10 —
" 5.....	Neut.	1690 "	11 + 12 —
	Ac.	1690 "	11 + 12 —
	Alk.	1690 "	11 + 12 —
" 6.....	Neut.	1020 "	10 + 11 —
	Ac.	1020 "	9 + 10 —
	Alk.	1020 "	10 + 11 —
" 7.....	Neut.	460 "	8 + 9 —
	Ac.	460 "	10 + 11 —
	Alk.	460 "	9 + 10 —
" 8.....	Neut.	1310 "	10 + 11 —
	Ac.	1310 "	10 + 11 —
	Alk.	1310 "	10 + 11 —

of the ferment, nevertheless, the variations were so slight as not to necessitate the bringing of all the specimens to a condition of neutrality, or to the same degree of acidity or alkalinity. Slight variations in the temperature of the water (from 37° to 40° C.) also showed a very slight influence on the activation of the ferment, as Wohlgemuth and others have shown, although obviously it is important to keep the bath at as constant a temperature (38° C.) as possible, for wide temperature variations have a marked effect.

In studying the diastase contents of the urine in pathological conditions, we found in a case of diarrhoea with fatty stool the limit was tube 9 (3000 units) ; in a case of post-operative gall-bladder fistula with normal pancreas also 9 (3000 units) ; in 2 cases of chronic pancreatitis with persistent jaundice, the common duct going through the head of the pancreas and being obstructed thereby, the limits were tubes 4 (500 units) and 6 (750 units) respectively ; in a case of advanced carcinoma of the pancreas with jaundice, tube 1 (333 units) ; in a case of pancreatic cyst, still draining, tube 7 (1000 units) ; in one no longer draining, tube 10 (6000 units) ; in a carcinoma of the œsophagus with marked asthenia and emaciation, but a

normal pancreas, tube 7 (1000 units) ; in an early carcinoma of the gall-bladder with normal pancreas, tube 9 (3000 units) ; in a case of chronic pancreatitis without jaundice, tube 8 (1500 units). All these diagnoses except the first were verified by operation. Thus it will be seen that in all cases with low readings the patient had either been deeply jaundiced for a long time, which unquestionably affects ferment production, although the early effects of bile are distinctly activating, or the disease from which they suffered was one associated with severe ill health and consequent lowering of the bodily functions, and thus none of the findings could be regarded as definitely diagnostic of pancreatic disease, although in some cases suggestive.

Durand (*Les Procédés d'Examen des Fonctions du Pancreas*) using another method for estimating the urinary diastase concluded that we should accord to the figures obtained in the urine only a relative value, although both Wohlgemuth and he call attention to the diagnostic value of high urine and low stool readings in the same case as suggestive of pancreatic retention due to stone in the pancreatic duct, etc.

Of course, the two main reasons why the quantitative determination of the urinary diastase is not diagnostic of pancreatic disease are, first, because of the widespread distribution of diastase in the body, and the possibility that in pancreatic disease there may be a vicarious increased diastatic activity of salivary glands and possibly of liver and muscles, and, second, because in renal diseases of various kinds there usually is a marked lessening of the urinary diastase irrespective of the condition of the pancreas and salivary glands, due to deficient renal permeability. For these reasons while a persistently low diastase content in the urine in the presence of normal kidneys is suggestive of pancreatic disease, yet the normal figures in our series are of much more value as a basis on which to study the renal function.

From these studies of the diastase content of the urine we may conclude that in healthy adults it falls within quite definite limits, and that markedly lessened amounts of this ferment in the urine, in the absence of renal changes, is suggestive of disturbance of pancreatic secretion, although not diagnostic ; but that the real value of these normal limits will be to furnish criteria in testing renal function by the diastase output in the urine.

NOTES ON NEW BOOKS.

A History of Laryngology and Rhinology. By JONATHAN WRIGHT, M. D. Second Edition. Revised and Enlarged. (Philadelphia and New York: Lea & Febiger, 1914.)

Dr. Wright's book, first printed without date some years ago, has been known from the time of the publication as the best history of laryngology and rhinology in English. It was preceded by the histories of Gordon Holmes (1885) and Paul Heymann (1896) and succeeded by Heymann's monograph of 1906 (*Puschmann's Handbuch*) and the huge five-volume work of Chauveau on the history of diseases of the pharynx (1901-6). The author has marred the individuality of his original edition by injudicious padding, and by the obtrusion of unnecessary expressions of opinion. This seems regrettable inasmuch as, for solid re-

search, this work is well worthy to take its place with such exhaustive treatises as those of Hirschberg on the history of ophthalmology or Adam Politzer's recent history of otology. Even if it should be bettered by some other work, it will always be invaluable to the nose and throat specialist for its detailed treatment of an extensive subject and for its accurate references. Beginning with the folklore and the history of the pre-Hippocratic period, the subject matter is well arranged (although there is no table of contents) and the style is readable. Special subjects, such as laryngoscopy or laryngeal paralysis, are well treated and the accounts of Horace Green and other leaders are what they should be. The index seems adequate. Some advantage in relation to perspicuity might have been gained by com-

pression here and there, but it would be invidious to pick flaws in a work which has already established its reputation for thoroughness and accuracy. The numerous bibliographical references deserve especial commendation, since their accuracy has been ascertained by Mr. Frank Place of the Library of the New York Academy of Medicine.

A Manual of Clinical Diagnosis. By CHARLES E. SIMON, M.D. Eighth Edition. Enlarged and thoroughly Revised. Illustrated. (Philadelphia: Lea & Febiger, 1914.)

This excellent book can be warmly endorsed on its eighth appearance, as being well up-to-date, and a most helpful guide for practitioners and students in their everyday work.

The Pathology of Growth: Tumors. By CHARLES POWELL WHITE, M.D., F.R.C.S. \$3.50. (New York: Paul B. Hoeber, 1913.)

In this volume the author presents the pathology of tumors with particular reference to the allied subjects of hypertrophy, regeneration, etc. He has laid stress upon the physiological aspect of the subject in the discussion of such questions as the relation between functional activity and growth and the origin, life history and causation of tumors. With the lack of any more precise knowledge concerning the etiology of tumors such a logical presentation of their origin based upon normal growth and regeneration and the relation of functional activity to growth must be commended. His theories are the ones that are gradually supplanting the older concepts and certainly offer the best means of giving the student an intelligent understanding of the important tumor problems. The book is so small that the discussion of the individual types of tumors is very brief. The illustrations are only relatively good. They are photomicrographs with a few minor exceptions. The book should prove of value to the student of pathology.

Prevention of Blindness No. 13: The Midwife in England. Being a Study of the Working of the English Midwives Act of 1902. By CAROLYN CONANT VANBLARCOM, R.N. With an Introduction by J. CLIFTON EDGAR, M.D., Professor of Obstetrics and Clinical Midwifery in the Cornell University Medical College, etc. (New York City: Committee for the Prevention of Blindness, 130 22d St., 1913.)

Recognizing the fact that the development of virulent ophthalmia among infants and consequent blindness was largely due to ignorant and untrained midwives, the Committee for the Prevention of Blindness in the State of New York sent Miss VanBlarcom to Europe to study the midwifery conditions of various countries. After an examination of the laws and methods of training midwives in fifteen countries of Europe, Miss VanBlarcom came to the conclusion that the conditions in England prior to the year 1902, when the midwifery law was enacted, were more nearly comparable to conditions in America than those of other countries and were remediable by a similar law. She points out the fact that since the enactment of the midwives act the percentage of deaths among infants in England has dropped from 161 per 1000, during 1901, to 106 per 1000 in 1910, and that the percentage of deaths from puerperal sepsis and accidents from childbirth from 4.65 per 1000, in 1901, to 3.69 per 1000 in 1909.

In England midwives attend about 50 per cent of all births and there are many schools where midwives can obtain excellent theoretical and practical instruction. When they are once trained, their work is carefully inspected and supervised and in the event of any failure to comply with the necessary regulations their license to practice is taken away. In the United States there is but a single school of high character, that recently established in con-

nection with Bellevue Hospital with a capacity of fifty pupils. The unfitness of many of the untrained women is shown by the following extract from Miss VanBlarcom's report:

"Although there are in America many competent midwives who have received careful training in European schools, reports from various parts of the country indicate that the majority of those practising here are dirty, ignorant and untrained. The extreme ignorance of some of the more unfit of these women is suggested by the superstitions which they foster; one, for example, will advise the mother to wear a string of bear's teeth to make the child strong; another that in case of tardy labor it is beneficial to throw hot coals on hen feathers and place them under the patient's bed; another that it is flying in the face of Providence to bathe the infant before it is two or three weeks old; while others recommend that such articles as cabbage hearts, bacon rinds, beer, etc., should be included in the baby's dietary. This type of midwife knows nothing of hygiene, asepsis or anti-sepsis and is often practically responsible for the death, blindness and mental and physical impairment of infants. Visits to the homes of these women fill one with dismay, for only too often one finds that a midwife, with a large practice, is herself a dirty, unkempt person living in a squalid tenement. A deplorably large group is exemplified by the old woman of 80 who declared, 'I am too old to clean; too weak to wash; too blind to sew; but, thank God! I can still put my neighbors to bed.'

"Only too often the American midwife assures her patient that it is natural for babies to have sore eyes, and she prescribes such remedies as milk, lemon juice, lard, raw potato, scraped beef, saliva, etc., and when the babies go blind, she piously declares that it is the will of God!"

The author states that at least 40 per cent of all births in the United States are attended by midwives. Her figures would seem to indicate a larger number as, e. g., San Francisco 25 per cent; Omaha 25 per cent; New York 39.2 per cent; Chicago 45 per cent; Toledo 51 per cent; New Orleans 70 per cent; St. Louis 75 per cent; Alabama 60 per cent; Maryland 40 per cent; Mississippi 80 per cent; Virginia 35 per cent; North Carolina 50 per cent; and Wisconsin 50 per cent.

In this country there is little or no law to regulate the practice of midwifery. They are allowed to practice without any restriction in thirteen states, and in fourteen there are no general laws relating to their training, registration or practice. Out of the remaining twenty-one states, twelve and the District of Columbia require that they shall pass an examination before receiving a license; six restrict attendance to normal cases; seven have irregular and inefficient laws; and two only, New York and Pennsylvania, have competent legislation.

Miss VanBlarcom declares very justly that midwives cannot be abolished or ignored. They must rather be educated, inspected, supervised and licensed. The details concerning the education of midwives in England are suggestive and instructive, and lead to an irresistible conclusion. Every lying-in institution furnishing the requisite amount of clinical material and possessing a competent medical staff should undertake the work of education. The pupil should have sufficient preliminary education to enable her to attend courses of instruction and practical work covering a period of from six to twelve months. She should be examined prior to receiving her license to practice and her work should be supervised by competent inspectors. All ignorant and uneducated women who are now midwives should be eliminated as rapidly as possible.

The author has presented an interesting chapter entitled, "Early History of English Midwives," which deserves to be expanded into a small volume. She also gives a history of the English Midwives Act of 1902. The agitation began in 1813 and dragged along until 1902, notwithstanding Miss Nightingale's

powerful influence in favor of a better training of midwives in 1860 and the introduction of bills regularly from 1879 until the final passage of the Midwives Act in 1902.

There are at present, in London alone, twenty-one lying-in hospitals licensed for the training of midwives.

There is also a careful chapter respecting the "Supervision of Midwives by Local Supervising Authorities," which indicates the careful safe-guards thrown about the practical working of the act. The author deserves much praise for her painstaking, thorough work and admirable report.

Arteriosclerosis. By LOUIS FAUGERES BISHOP, M. D. \$3.50. (London: Henry Frowde and Hodder & Stoughton, 1914.)

Dr. Bishop's theory is that arteriosclerosis is due to a sensitization of individuals to particular proteins, or, to split products of particular proteins, rather than to any of the more commonly attributed causes, *e. g.*: alcohol, syphilis, worry, etc. His cure for the trouble is then what he calls a "few-protein" diet; that is, limiting the patient to one, rather than several, forms of protein, on the theory of chances that out of the large number of existing proteins the one to which the patient is sensitized will not be selected. Overfeeding has long been considered a possible cause of arteriosclerosis and it is difficult to distinguish in essentials this theory from that of the author, since in both instances the results must be due to faulty metabolism.

The work is over long, and is not a vital contribution to the subject. It is to be regretted that Dr. Bishop did not limit himself and write a much briefer essay, which would have been most helpful to the general practitioner.

Asthma and Its Radical Treatment. By JAMES ADAM, M. D. \$1.50. (New York: Paul B. Hoeber, 1914.)

In this small volume the author enlarges the thesis written for his medical degree to show that asthma is due to a toxæmia of the intestines or tissues, following too abundant ingestion of carbohydrates, leading to errors in proteid metabolism. His work is based entirely on clinical observations, for he has had no opportunity to do any experimental work. He believes that certain pathological nasal conditions may provoke attacks of asthma, but that these play a very secondary rôle; and he thinks that the prevalent theory that asthma is a neurosis is quite wrong. The work cannot be considered important in elucidating the obscure origin of asthma, since the author's evidence is not strong and convincing, though all will agree that errors of digestion may induce attacks of asthma in those liable to this disease.

Guide to the Microscopic Examination of the Eye. By PROFESSOR R. GREEFF. Translated from the Third German Edition by HUGH WALKER, M. B. \$2. (New York: Paul B. Hoeber, 1914.)

The pathologist, who is especially interested in the eye, has no better book than this in English to assist him in his work. Here he will find full and clear descriptions of all the steps that must be taken to examine this organ microscopically, and with this guide he can study the eye as readily as the other organs of the body. It is a work of very great value.

Diseases of the Rectum and Anus. By HARRISON CRIPPS, F. R. C. S. Fourth Edition. \$3.25. (New York: The Macmillan Company, 1914.)

This work, which reappears as the fourth edition, can scarcely be considered a modern surgical treatise. The spirit and tone of the first edition, which in part dates back to 1875, are still manifest. The arrangement of the book is similar to that of the various other text books and monographs on the same subject;

beginning with chapters on anatomy and methods of examination, then treating the simpler surgical conditions in separate chapters and concluding with a more extensive consideration of cancer of the rectum. In the first chapter of the book the curious failure of the author to assimilate modern conceptions of pathology is rendered conspicuous by his theory as to the relation between the epithelial cells and the leucocytes. It cannot fail to strike one as grotesque to see advanced the hypothesis that epithelial cells may be derived from leucocytes, and *vice versa*, and to learn that the liver metastases are due to leucocytes lodged in the liver and then resuming the characteristic of their parents, the epithelial cells. It is quite evident that the author does not distinguish, histologically at least, between inflammation and new growth.

The second chapter, dealing with methods of examination, is similarly antiquated. No mention is made of the improved methods of electrical illumination and exploration of the upper rectum and sigmoid. Indeed, instrumental methods of examination are mentioned only to be condemned and digital touch is practically the only procedure recommended for internal examination.

The treatment of the particular subjects of clinical nature, such as hemorrhoids, fistulæ, abscess, etc., is decidedly more valuable than the more general and abstract parts of the book, but here again one is constantly impressed with the diffuse and unscientific attitude of the author. There is much repetition and lack of concise statement and the larger surgical procedures which have of late been most extensively used receive but secondary attention. For instance, the more radical methods of treatment of ulcerated conditions by colostomy and appendicostomy are not mentioned at all; scattered through the book, however, are helpful suggestions and many shrewd and very human comments. The following paragraph seems worthy of quotation as typifying the good sense but unscientific flavor of the whole work.

"Of all disagreeables in a surgical practice, nothing comes up to a midnight recurrent hæmorrhage from one of your own operations. It nearly always occurs on a wet night when you are dead tired, the patient is anxious, and the friends alarmed, and there is never any extra fee, a combination of evils which, by proper care, may be avoided by securing everything before the patient is put back to bed."

In short the work is that of a successful and experienced man whose attempts at scientific explanations do not strengthen the value of his contributions. The chief claim of the book to notice is the fact that it contains the author's Jacksonian Prize Essay of 1875 on "Cancer of the Rectum," and his opening address on the same subject delivered at the meeting of the British Medical Association in Liverpool in 1912. As the basis of these two noteworthy contributions there are presented 445 personal cases of cancer of the rectum. This remarkable body of personal experience is well analyzed from a number of viewpoints and furnishes data of importance to any one interested in this subject. One cannot fail to see from reading these articles the important part which Cripps has played in the development of the present surgical methods of attack on rectal cancer. This is particularly true of the introduction of colostomy for the palliative treatment of this condition. But here again one finds little attention paid to the so-called combined approach which is now being employed by the leaders of surgical advance in Europe and America and one is struck by the fact that the old tangential colostomy is given entire preference over the transverse method which is, however, usually considered a better procedure where permanent drainage must be established. The last portion of the book is characteristic of the chief value of the whole work, for here one finds collected a most interesting and extensive series of cases in which a communication has arisen between the bladder and some portion of the intestinal tract.

American Association for Study and Prevention of Infant Mortality. Transactions of the Fourth Annual Meeting. Washington, D. C., 1913.

The importance of this association is very great and this volume of transactions contains many papers of value on a large variety of topics intimately connected with the saving of the lives of infants. There were special sessions devoted to discussions of nursing and social work, pediatrics, eugenics, obstetrics, vital and social statistics, and general sessions in which other problems were taken up. The association has made good progress and it is to be hoped that it will not lack for large and generous support.

Practical Bacteriology, Microbiology and Serum Therapy (Medical and Veterinary). A Text-Book for Laboratory Use. By DR. A. BESSON. Translated by H. J. HUTCHINS, D.S.O., etc. (London: Longmans, Green and Co., 1913.)

The text-book of Practical Bacteriology by Besson, since its first appearance in 1897, has enjoyed a great popularity among French-speaking people in consequence of which an English edition has been prepared by Dr. H. J. Hutchins of the University of Durham, who has also added several notes of his own to make it more complete for the English reader. The present edition is well illustrated and systematically arranged so that the subject matter is easily accessible. While designed especially to serve as a laboratory guide it would seem more suitable for the advanced student than for the beginner. Like many other text-books written by the French microbiologists this one of Besson has a very incomplete bibliography and insufficient credit is given investigators outside of France, even when the fundamental researches have been contributed by them. At the same time a new system of nomenclature has been introduced and a rearrangement of certain bacteria and moulds affected which can hardly be regarded as justifiable. As a result the subject matter often affords the reader confused ideas of an already confused subject. Despite its faults, however, the book is admirable and should prove of great value to students of the subject. It is divided into seven parts, each of which is further subdivided into subdivisions, chapters and sections. The headings of these various parts indicate the general scope of the book and are as follows: General technique, pathogenic bacteria, parasitic fungi, pathogenic spirochætæ, protozoan parasites, filterable viruses and bacteriological examination of water sewage and air. Each part deserves special mention. Part I gives a complete description of the principles, methods and apparatus used in sterilization, media making, staining bacteria, animal experimentation, and the isolation and study of microorganisms. In this part the essentials of technique are carefully presented and are, moreover, made interesting by an ample consideration of their historical development. The plan of recommending certain particular methods, while giving the reader the benefit of the vast experience of the author, is open to some objection, since it may make the reader skeptical of the value of the other methods described. A most instructive chapter on the microscope, explaining its physical and mathematical properties, is included in this part and an especially good chapter at the end on immunity.

Part II consists of a very complete consideration of the pathogenic bacteria. Each organism is treated in this detailed fashion: Distribution, experimental inoculation, effect upon susceptible animals, morphology, staining and cultural characteristics, biological properties and serum therapeutics. The discussion of the serum therapy of the individual organisms is accurate and complete and great stress is laid upon the various complications which occasionally arise in the care of patients. The methods of collecting samples, the properties of the serum, and the proper interpretation of the various findings are throughout well described.

The chapter on *Bacillus tuberculosis* is especially to be commended. It gives in detail the findings of the English Commission (1901), together with the earlier work on this subject. In this part, however, confusing nomenclature is constantly met with and the authors show themselves hopelessly ignorant of the scientific rules governing this subject. New terms of debatable value, such as *Pasteurella* and *Salmonella*, are constantly introduced and at the same time names are employed for microorganisms which are neither the correct name nor the commonly-accepted name. For instance, the hog cholera bacillus is arbitrarily called the *Bacillus enteridites ortrycke*, and it is difficult to understand by what process of reasoning the authors feel justified in such a procedure. Again the anærobic bacillus first described by Dr. Welch as the cause of emphysematous gangrene is said to be identical with an organism described years later by a French observer and the name employed by this latter observer, *Bacillus perfringens*, has been adopted as the name of the organism. The description of the other anærobic bacteria in this part is, however, satisfactory in the main, and the importance of the pathogenic anærobes to the veterinary surgeon well brought out.

Part III, in which the parasitic fungi are considered, likewise gives a mass of detailed information of great value. It has, however, again the disadvantage of employing a new nomenclature, and the classification of Blanchard, which is not universally recognized, is followed throughout. Little credit is given the men who have done the fundamental work on this subject. Wright's name is barely mentioned in the consideration of actinomycosis and MacCallum's in relation to the "asteroides." The parasitic spirochætæ are well, though briefly, described, in Part IV and the latest theories in regard to them outlined. The chapter on *Treponema pallidum* is of great interest, and in it accurate methods are outlined for the differentiation of this organism from other spirochætæ by means of morphological characteristics and special stains. The discussion on the nature of the serum-diagnosis of syphilis is striking and the explanation of the reaction from the chemical side and its reproduction through chemical agents, apt. Part V on the protozoan parasites is also to be commended, since it gives the reader a clear conception of some of the complications which may be met in the field of tropical medicine. Filterable viruses are briefly described in Part VI, and in this part the work of American investigators, such as Flexner and Lewis, Anderson and Goldberger, Rickets and Wilder, has received ample consideration. Part VII, in which the application of bacteriological methods to the examination of water and air is considered, forms the closing chapter of the book and cannot be said to have any value. The methods described are antiquated and are of only historical interest to the modern hygienist.

Therapeutics of the Gastro-Intestinal Tract. By DR. CARL WEGELE. Adapted and Edited with Additions by DR. MAURICE W. GROSS and DR. I. W. HELD. (New York: Rebman Company, 1913.)

This book of over three hundred pages gives in a very concise form the therapeutics of digestive diseases in the light of our most modern conceptions of the subject.

The book is not simply a translation, for the editors have made extensive additions to the German work; they have amplified the diagnostic side of the various diseases; they have added a separate chapter on diseases of the œsophagus, diseases of the pancreas, the X-ray diagnosis of gastro-intestinal diseases, the duodenal tube, the last based very considerably on their own researches in the field, parasitic diseases, and diseases of the intestinal blood-vessels. The translation in the main is a very good one, and the general arrangement satisfactory. A short chapter on general diagnosis precedes the main body of the work, that devoted to treatment and, in this preliminary chapter, although a short one, we find most of the modern methods of gastro-intestinal

diagnosis touched upon, the chemical and biological tests being brought quite up to date (1913).

Especial commendation can be given to the first of the chapters devoted to treatment in which general principles are discussed. The principles of diet are discussed in very considerable detail, while much space is devoted to directions for the preparation of dishes for special dietetic purposes; physical treatment is handled in a satisfactory manner, as also medical treatment, while a few words are added as to the surgical treatment of digestive disorders.

The next chapters are devoted to the special therapy of the gastro-intestinal diseases, much attention being paid to the disturbances of tone and motility, and to the nervous affections of this organ.

The same general method is applied to the consideration of the diseases of the intestines: First, a brief discussion of the methods of diagnosis employed, then an outline of the treatment employed in the various diseases, distinct stress being laid on intestinal ulcerations, inflammations, neoplasms, and appendicitis, while the translators have added here sections on diseases of the intestinal blood vessels and intestinal parasites.

The chapters on the duodenum and on the diseases of the pancreas are not in Wegele's book, but are also supplied by the translators, and the latter is of especial value, as many of the newer functional pancreatic tests are considered.

The last chapter is also one not found in the original—one devoted to X-ray diagnosis of the gastro-intestinal tract, and, of course, essential to any book on digestive diseases in the light of modern methods of diagnosis.

The book is practical, but not too practical—in it are gathered together many important facts, methods of diagnosis and of treatment not found in the usual works, and only to be gotten, as a rule, by careful analysis of the literature, and we can thoroughly recommend it as an excellent exposition of the subject.

B.

Lectures on Dietetics. By MAX EINHORN, M. D. \$1. (New York: Paul B. Hoeber, 1914.)

This is a very slight work, which can be read through in a couple of hours. It does little more than touch the surface of this important branch of medicine, but it will serve for one who wants merely to get an idea of the general principles underlying the subject.

Medical Gynecology. By SAMUEL WYLLIS BANDLER, M. D., etc. Third Edition. Thoroughly Revised. Illustrated. \$5. (Philadelphia and London: W. B. Saunders Company, 1914.)

The more gynecology is studied from a medical, rather than a purely surgical, point of view, the better, for the lives of many women have been sacrificed to quite needless operations. For the general practitioner this gynecology is a most valuable book and the author's new edition comes at an opportune moment, when surgeons are gradually recognizing that less operations, rather than more, should be the watchword of the day. The great art of surgery is to know when not to operate and Dr. Bandler's Medical Gynecology will show the student how much can be accomplished by other means than the knife.

Treatise on Diseases of the Skin. By HENRY W. STELWAGON, M. D., etc. Seventh Edition. Thoroughly Revised. Illustrated. \$6. (Philadelphia and London: W. B. Saunders Company, 1914.)

The specialist in skin diseases cannot do without this work and will want to have the last edition, which contains much not in the sixth, both in the way of text and illustrations. The excellence of this treatise was early recognized, and there is no doubt that the book will long continue to hold its place in the first rank.

A Short Practice of Midwifery for Nurses. By HENRY JELLETT, M. D. (Dublin University), etc. Fourth Edition. Revised. Illustrated. \$2.50. (New York: Paul B. Hoeber, 1914.)

This text-book is based on the teaching in the famous Rotunda Hospital, and has been a favorite work abroad, and deserves its popularity. For nurses in general hospitals, where but few maternity cases are seen, it is somewhat too comprehensive, but for nurses in lying-in hospitals it is excellent, though whether it is wise for nurses to make vaginal examinations of one sort or another as they are taught to do in Dublin may be seriously questioned, unless they intend to be midwives. The author writes well and his book can be profitably studied by students as well as nurses.

Surgery of the Vascular System. By BERTRAM M. BERNHEIM, M. D. Illustrated. \$3.00. (Philadelphia and London: J. B. Lippincott Company, 1913.)

In order to prepare a good monograph the writer must have a complete knowledge of the work done by others and be able to select the essential points from such work; he must have a practical working knowledge of the subject, that is, he must have done work such as he describes; and, lastly, he must have made original researches in the field in order that he may be able to speak authoritatively on the disputed points. All these qualifications the author possesses.

As stated in the preface, this book deals, not so much with that portion of vascular surgery which is treated of in the ordinary text-books, but with the new and strikingly brilliant methods and applications of blood-vessel suturing. The text is concise, clear and eminently practical. It is seldom that one has the opportunity to read a work so discernedly shorn of useless and cumbersome material, and in which the essential points are so especially emphasized, and the working principles so clearly outlined. It tells just what has been done in this field and gives such a clear description of the method that any one who is prepared for skilful surgery can follow it.

The book contains ten chapters: General Technique, Transfusion, End to End Suture, Lateral Anastomosis, Transplantation of a Segment of a Vein or Artery, Arteriovenous Anastomosis, Reversal of the Circulation, Varicose Veins, Surgery of the Heart, Aneurisms and Statistical Study of the Treatment of Aneurisms.

In his chapter on Transfusion, Bernheim gives a description of two of the more important methods—Crile's and Elsberg's—and then proceeds to describe his own, pointing out the salient points in each and showing how the author's method has overcome some of the defects in the others. He speaks enthusiastically of the possibilities of transfusion and thinks that its field may be very greatly increased. While admitting that hemolysis should not be entirely overlooked, he believes that the danger is so remote that it is not necessary to take it into serious consideration. His own method of transfusion is beyond question much simpler and much easier to execute than the others, while at the same time it offers advantages equal in every way.

The author's method of lateral anastomosis is simpler and superior to the methods of Carrel, Hadda and Jeger. He has shown by repeated operations on the human subject the practicability and value of this procedure.

In his chapter on the Reversal of the Circulation, he shows beyond question by his operation on human beings that the blood can be sent down the veins in spite of their valves, and that a real reversal occurs. He has operated in several cases of Reynaud's disease and proven conclusively by the cure of the patients and the re-establishment of a good circulation that such a reversal does occur.

In his chapter on Varicose Veins he simply mentions these various procedures and gives short descriptions, inasmuch as all of these operations are given in the usual text-books.

His Surgery of the Heart is contained in three pages, a sufficient allowance, because in reality there is no surgery of the heart.

In his chapter on Aneurisms we find useful and practical analysis of the literature, which enables us to find in a moment the operations which have been done on different arteries and the results obtained.

Bernheim very properly states that any one who wishes to take up this line of work must first have mastered the fundamental principles of surgery and also have done a large number of experiments on animals. With this view every one must most heartily concur. It is true that from a casual reading of this book one might gather that the procedures were easy, but the fact must not be overlooked that they are easy only after the surgeon has mastered a number of points of technique and detail which make for success or failure, and certainly no one is justified in undertaking them on human subjects until he has thoroughly mastered the details on animals.

Blood vessel surgery is one of the most brilliant and practical chapters in modern surgical advance—most practical because it is beyond question immediately life-saving, and is a procedure that may be called for at any time and at any place. Every man, therefore, who is doing surgery, is not just to his patients unless he himself can do this work or has some one at hand who can do it. Severe hemorrhages occur any time and anywhere. For such, in many instances, there is only one effective remedy, namely, transfusion. It means the saving of life and unless the surgeon can do this or have it done he is responsible for the patient's death.

The style of the book is concise, clear and scholarly. The illustrations, fifty-three in number, do justice to one of Max Broedel's pupils. Taken as a whole it is a distinct contribution to the literature and a practical treatise that no surgeon can afford to be without.

Man's Redemption of Man and A Way of Life. By WILLIAM OSLER. \$1. (New York: Paul B. Hoeber, 1914.)

Every medical student should own and read these essays till he knows them by heart, or at least until their import has been fully and completely realized by him. The lessons of life, as taught by Sir William Osler, will make life finer and brighter for us all, and not only medical students, but any thoughtful reader will enjoy these lectures and be the better for having read them.

The Principles and Practice of Gynecology for Students and Practitioners. By E. C. DUDLEY, A. M., M. D. Sixth revised edition. Illustrated. (Philadelphia and New York: Lea & Febiger, 1913.)

One is impressed with a review of this book that it reflects the work of a man of wide experience and sound judgment.

In his introduction the author recognized the inevitable expansion of gynecology, the most important of the medical specialties, into the broader field covering all of abdominal surgery. He warns the general surgeon, the "tyro operator," and the gynecologist himself, that the problems of the diseases peculiar to women are by no means settled, and that no one should enter this field as an operator who is unwilling to undergo the long and careful training that gives special judgment and skill in managing these important problems.

Like the former editions this one is arranged to bring the chief subjects before the student in their pathological and etiological relationships. For instance, infections and inflammations are so grouped as to treat consecutively of vulvovaginitis, metritis, salpingitis, oophoritis, and peritonitis; or, in other words, in the sequence in which they often occur. In like manner tumors of the various organs are treated of in consecutive chapters, traumatism in another section of the book, and displacements in another.

Moderation and sanity mark the author's recommendations in medical or office gynecology as well as in the portions of his work dealing with the operative side of this specialty.

In his chapter on the relations of dress to the diseases of women, the author probably lays too much stress on the corset as a molder of form and omits a discussion on the congenital variations of form and waist line in different individuals.

While the illustrations for the most part are crude, they are easy of interpretation and the work is adequately illustrated.

The Junior Nurse. By CHARLOTTE A. BROWN, R. N. \$1.50. (Philadelphia and New York: Lea & Febiger, 1914.)

Junior nurses, who need an introduction to nursing, will find Miss Brown's book helpful. It is extremely difficult to write a really good elementary text-book of any sort, but, on the whole, Miss Brown has accomplished her task satisfactorily.

Oxford Medical Publications: A Handbook for the Post-Mortem Room. By ALEXANDER G. GIBSON, D. M. (Oxon.), etc. \$1.50. (London: Henry Frowde and Hodder & Stoughton, 1914.)

Few students are sufficiently carefully instructed in the making of autopsies, and to those who want to really know how to perform an autopsy well we recommend this small work heartily; it is a most serviceable guide, for the author's directions are clear, and the ground is thoroughly covered. There is no better book of its size and kind.

Dysenteries: Their Differentiation and Treatment. By LEONARD ROGERS, M. D., etc. (London: Henry Frowde and Hodder & Stoughton, 1913.)

The principal object of this work, as the author states in his preface, is the differentiation and therapy of bacillary and amebic dysentery. Dysenteric symptoms due to other protozoa and to helminthes are considered as well as hill diarrhoea and sprue.

The introductory chapter is given over to an interesting discussion of the history of dysentery before the differentiation between the bacillary and amebic types. Some important references are given to the work of the French school on this differentiation before its final establishment by Shiga in 1898. Extreme conservatism is shown in the opinions expressed both upon the cultivability and the species differentiation of the parasitic entamoebæ. The two pathogenic species, *E. histolytica* and *E. tetragena*, are retained and some emphasis is laid upon the minute differences between them according to the original descriptions of Viereck and Hartman, although these two species are considered to be identical by many protozoologists.

The advantages of emetine are discussed thoroughly. Valuable details are given in regard to the use of emetine for the radical cure of dysentery and hepatitis. It is important to note that in special cases adults may be given as much as three grains subcutaneously in one day and one grain intravenously at one injection. Two patients are reported in whom complete sterilization of the tissues was obtained. Rogers expresses an optimistic opinion in regard to the radical cure of chronic cases.

In the north, in the United States, where the chronic cases predominate, relapses after a few months are very frequent, though the relief of the acute symptoms has been very satisfactory. In this connection it must be emphasized that the dosages used in the United States are often smaller than those recommended by Rogers.

The Early Diagnosis of Tubercle. By CLIVE RIVIERE, M. D., etc. (London: Henry Frowde and Hodder & Stoughton.)

An excellent little manual on the early diagnosis of pulmonary tuberculosis. Although everything of importance is included, still the matter is carefully selected and judiciously appraised. It will serve students and practitioners as a reliable guide.

BOOKS RECEIVED.

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- Innere Sekretion und Schwangerschaft.* Von Professor Dr. L. Seitz. Mit 6 farbigen Tafeln. 1913. 8°. 256 pages. Johann Ambrosius Barth, Leipzig.
- Handbuch der Frauenheilkunde.* Herausgegeben von C. Menge und E. Opitz. Mit 374 zum Teil farbigen Abbildungen im Text. 1913. 8°. 802 pages. J. F. Bergmann, Wiesbaden.
- Die Struktur der Geschlechtsorgane der Haussäugetiere mit anatomischen Bemerkungen.* Von Dr. med. vet. Reinhold Schmaltz. Mit 168 Textabbildungen. 1911. 8°. 388 pages. Paul Parey, Berlin.
- The Physiology of Reproduction.* By James H. A. Marshall, M. A. (Cantab.), D. Sc. (Edin.). With a Preface by Professor E. A. Schäfer, Sc. D., LL. D., F. R. S., and Contributions by William Cramer, Ph. D., D. Sc., and James Lochhead, M. A., M. D., B. Sc., F. R. C. S. E. With illustrations. 1910. 8°. 706 pages. Longmans, Green and Co., London, New York, Bombay and Calcutta.
- On Diseases of the Rectum and Anus.* Including the Sixth Edition of the Jacksonian Prize Essay on Cancer. Fourth edition. Reprinted to include the Opening Address on the Surgical Treatment of Rectal Cancer, delivered at the Annual Meeting of the British Medical Association, Liverpool, 1912. By Harrison Cripps, F. R. C. S. 1914. 8°. 588 pages. Macmillan Company, New York.
- Diagnostic Methods.* A Guide for History Taking, Making of Routine Physical Examinations and the Usual Laboratory Tests Necessary for Students in Clinical Pathology, Hospital Internes and Practicing Physicians. By Herbert Thomas Brooks, A. B., M. D. Second edition, revised and rewritten. 1914. 8°. 82 pages. C. V. Mosby Company, St. Louis.
- Practical Sanitation.* By Fletcher Gardner, M. D., and James Persons Simonds, B. A., M. D. Illustrated. 1914. 8°. 403 pages. C. V. Mosby Company, St. Louis.
- Diagnosis in the Office and at the Bedside.* The use of Symptoms and Physical Signs in the Diagnosis of Disease. By Hobart Amory Hare, M. D., B. Sc. Seventh edition, thoroughly revised. Illustrated with 164 engravings and 10 plates. 1914. 8vo. 547 pages. Lea & Febiger, Philadelphia and New York.
- Infections of the Hand.* A Guide to the Surgical Treatment of Acute and Chronic Suppurative Processes in the Fingers, Hand and Forearm. By Allen B. Kanavel, M. D. Second edition, thoroughly revised. Illustrated with 147 engravings. 1914. 8°. 463 pages. Lea & Febiger, Philadelphia and New York.
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- The Anatomist's Notebook.* A Guide to the Dissection of the Human Body. By A. Melville Paterson, M. D. (Edin.), F. R. C. S. (Eng.). 1914. 8°. 349 pages. Henry Frowde, London; Hodder & Stoughton, London.
- The Unconscious.* The Fundamentals of Human Personality, Normal and Abnormal. By Morton Prince, M. D., LL. D. 1914. 12°. 549 pages. The Macmillan Company, New York.
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- Pharmacology, Clinical and Experimental.* A Groundwork of Medical Treatment. By Dr. Hans H. Meyer and R. Gottlieb. Authorized translation into English by John Taylor Halsey, M. D. With 65 text illustrations, 7 in color. 1914. 8°. 604 pages. J. B. Lippincott Company, Philadelphia and London.
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- Modern Medicine: Its Theory and Practice.* In Original Contributions by American and Foreign Authors. Edited by Sir William Osler (Bart.), M. D., F. R. S., and Thomas McCrae, M. D. Volume II. *Diseases caused by Protozoa and Animal Parasites. Diseases due to Physical, Chemical and Organic Agents. Diseases of Metabolism and of the Respiratory System.* Second edition, thoroughly revised. Illustrated. 1914. 8°. 1144 pages. Lea & Febiger, Philadelphia and New York.
- Ionic Medication.* The Principles of the Method and an Account of the Clinical Results Obtained. By H. Lewis Jones, M. D. Second edition. 1914. 12°. 155 pages. P. Blakiston's Son & Co., Philadelphia.
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- Immunity. Methods of Diagnosis and Therapy and their Practical Application.* By Julius Citron. Translated from the German and edited by A. L. Garbat, M. D. Second edition, revised and enlarged, 30 illustrations, 2 colored plates and 8 charts. 1914. 8vo. 267 pages. P. Blakiston's Son & Co., Philadelphia.

- Tuberculosis: Its Cause, Cure and Prevention.* A revised edition of "The Great White Plague." By Edward O. Otis, M. D. 1914. 12°. 326 pages. Thomas Y. Crowell Company, New York.
- Therapeutics of the Circulation.* By Sir Lauder Brunton, Bt. M. D., D. Sc., LL. D. (Edin.), LL. D. (Aberd.), F. R. C. P., F. R. S. Second edition. With illustrations. 1914. 12°. 536 pages. John Murray, London.
- Les Nouveaux Horizons de la Science.* Par H. Guilleminot. Tome troisième. *La Matière Vivante, sa Chimie—sa Morphologie.* 1914. 12°. 429 pages. G. Steinheil, Paris.
- A Manual of Clinical Diagnosis by Means of Laboratory Methods.* By Charles E. Simon, B. A., M. D. Eighth edition, enlarged and thoroughly revised. Illustrated with 185 engravings and 25 plates. 1914. 8°. 809 pages. Lea & Febiger, Philadelphia and New York.
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- Some American Medical Botanists. Commemorated in our Botanical Nomenclature.* By Howard A. Kelly, M. D., LL. D. 1914. 8vo. 215 pages. Southworth Company, Troy, New York.
- The South African Institute for Medical Research. Memoir No. I. An Enquiry into the Etiology, Manifestations and Prevention of Pneumonia amongst Natives on the Rand, Recruited from Tropical Areas.* By G. D. Maynard, F. R. C. S. E. 1913. 4°. 101 pages. W. E. Hortor & Co., Johannesburg.
- Man's Redemption of Man.* A Lay Sermon, McEwan Hall, Edinburgh, Sunday, July 2, 1910. By William Osler. 1913. 24°. 63 pages. Paul B. Hoeber, New York.
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- A Reference Handbook of the Medical Sciences.* Embracing the entire range of Scientific and Practical Medicine and Allied Science. By various authors. First and second editions edited by Albert H. Buck, M. D. Third edition completely revised and rewritten. Edited by Thomas Lathrop Stedman, A. M., M. D. Complete in eight volumes. Volume three. Illustrated by numerous chromolithographs and six hundred and sixty-five half-tone and wood engravings. 1914. 4°. 930 pages. William Wood & Co., New York.
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- Treatment of Neurasthenia.* By Dr. Paul Hartenberg. Translated by Ernest Playfair, M. B., M. R. C. P. 1914. 12° 283 pages. Henry Frowde and Hodder & Stoughton, Edinburgh, Glasgow and London.
- Lectures on Dietetics.* By Max Einhorn. 1914. 12°. 156 pages. Paul B. Hoeber, New York.
- The Junior Nurse.* By Charlotte A. Brown, R. N. Illustrated. 1914. 12°. 208 pages. Lea & Febiger, Philadelphia and New York.
- Papers on Diabetes Mellitus, Acidosis, etc.* By T. Stuart Hart, A. M., M. D. 1903-1912. 8°. New York.
- Treatise on Diseases of the Skin.* By Henry W. Stelwagon, M. D., Ph. D. Seventh edition, thoroughly revised. With 334 illustrations in the text, and 33 full-page colored and half-tone plates. 1914. 8°. 1250 pages. W. B. Saunders Company, Philadelphia and London.
- Medical Gynecology.* By Samuel Wyllis Bandler, M. D. Third edition, thoroughly revised. With original illustrations. 1914. 8°. 790 pages. W. B. Saunders Company, Philadelphia and London.
- Development and Anatomy of the Nasal Accessory Sinuses in Man.* Observations Based on Two Hundred and Ninety Lateral Nasal Walls, Showing the Various Stages and Types of Development of the Accessory Sinus Areas from the Sixtieth Day of Fetal Life to Advanced Maturity. By Warren B. Davis, M. D. 1914. 8°. 172 pages. W. B. Saunders Company, Philadelphia and London.
- The Practice of Pediatrics.* By Charles Gilmore Kerley. Illustrated. 1914. 8°. 878 pages. W. B. Saunders Company, Philadelphia and London.
- The Principles of Pathologic Histology.* By Frank B. Mallory, M. D. With 497 figures containing 683 illustrations, 124 in colors, and all but two original printed directly in the text. 1914. 8°. 677 pages. W. B. Saunders Company, Philadelphia and London.
- Chemical Pathology.* Being A Discussion of General Pathology from the Standpoint of the Chemical Processes Involved. By H. Gideon Wells, Ph. D., M. D. Second edition, thoroughly revised. 1914. 8°. 616 pages. W. B. Saunders Company, Philadelphia and London.
- A Short Practice of Midwifery for Nurses.* Embodying the Treatment Adopted in the Rotunda Hospital, Dublin. By Henry Jellett, B. A., M. D. (Dublin University), F. R. C. P. 1. Fourth edition, revised. With six plates and 169 illustrations in the text, also an appendix, a glossary of medical terms, and the regulations of the Central Midwives Board. 1914. 12°. 508 pages. Paul B. Hoeber, New York.
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- Fiske Fund Prize Dissertation. No. LV. Etiology, Pathology and Treatment of Phlebitis.* By W. Louis Chapman, M. D. 1913. 8°. 86 pages. Providence, Rhode Island.
- Manhattan Eye, Ear and Throat Hospital Reports.* Number XV. Edgar S. Thomson, M. D., Wendell C. Phillips, M. D., and Harmon Smith, M. D., Editors. February, 1914. 8°. 323 pages. New York.
- Public Health Reports.* Issued in weekly numbers by the United States Public Health Service. Volume XXVIII, part 1, numbers 1-26. January-June, 1913. 8°. 1402 pages. Government Printing Office, Washington.
- Blood-Pressure Primer.* The Sphygmomanometer and its Practical Application. By Francis Ashley Faught, M. D. Containing one full-page plate and numerous explanatory diagrams in the text. 1914. 12°. 121 pages. G. P. Pilling & Son Co., Philadelphia.

THE QUARTER CENTENNIAL ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL AND THE TWENTY-FIRST ANNIVERSARY OF THE OPENING OF THE MEDICAL SCHOOL

Will be observed by appropriate exercises beginning October 5, 1914, and continuing during the week.

The exercises upon Monday, October 5, 9.30 a. m. to 12 m., are to be especially arranged for by the Training School for Nurses and will be announced later.

Upon Monday at 2 p. m., the formal opening meeting will be held at the Lyric, with addresses by Dr. W. H. Welch, Sir William Osler, Miss M. Adelaide Nutting and Dr. H. M. Hurd.

At 5 p. m. there will be a garden party upon the lawn at the Hospital.

In the evening there will be dinners of the former Medical Officers of the Hospital, and of the Alumnae of the Training School for Nurses.

Upon Tuesday, October 6, 9.30 a. m. until 12 m., papers upon medicine by former members of the staff will be presented in the Medical Amphitheatre. Papers or demonstrations of methods of study of Psychiatry at the Henry Phipps' Clinic from 10 a. m. to 12 m. Gynecological operations in the Surgical Amphitheatre from 10 a. m. until 1 p. m. A Clinic by Sir William Osler at 12 m.

Luncheon at the Hospital from 1 to 2.30 p. m.

From 2.30 to 3.30 p. m. Clinic in the Harriet Lane Home by Dr. John Howland. At 3.30 p. m., a dedication of the Hewetson Medallion.

A demonstration of Nurses' work in the Medical Amphitheatre from 4 to 5 p. m.

From 4.30 to 5.30 p. m., a lecture on the Herter Foundation by Dr. Thomas Lewis of London.

A ladies' Garden Party upon the lawn of the Hospital at 5 p. m.

In the evening a Dinner of the Alumni of the Medical School.

Wednesday, October 7, from 9.30 a. m. to 1 p. m., Surgical Operations in the Surgical Amphitheatre. Also from 9.30 a. m. to 11 a. m. Medical Visits to Wards.

From 11 a. m. to 1 p. m. Visits to Medical Laboratories.

1 p. m., Luncheon.

At 3.30 p. m., Dedication of the James Buchanan Brady Urological Clinic, with addresses by Dr. Winford Smith, President Goodnow of The Johns Hopkins University, Dr. H. H. Young, and others.

In the evening a Subscription Dinner to Mr. James Buchanan Brady. Also Class Dinners.

Thursday, October 8, 9.30 a. m. to 1 p. m., Papers in Pathology in the Medical Amphitheatre.

Also Papers or Addresses upon Obstetrical Topics in the

Surgical Lecture Room, 10 a. m. to 12 m. Operations in Urological Surgery in the Surgical Amphitheatre, 10 a. m. to 12 m. 1 to 2.30 p. m., Luncheon.

4.30, Second Herter Lecture by Dr. Lewis.

In the Evening, Class Dinners.

Friday, October 9, 4.30 p. m., Third Herter Lecture by Dr. Lewis.

More detailed programmes will be published later.

PROGRAMME FOR THE CELEBRATION OF THE TWENTY-FIFTH ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL

MONDAY October 5	TUESDAY October 6	WEDNESDAY October 7	THURSDAY October 8
Nurses' Day	9.30-12 Medicine (Medical Amphitheatre) Psychiatry 10-1 Gynecology (Surgical Amphitheatre) 12 Clinic Sir William Osler	9.30-1 Surgery (Surgical Amphitheatre) 9-11 Medical Visits 11-1 Medical Laboratories	Pathology (Medical Amphitheatre) Obstetrics (Surgical Lecture Room) 10-12 Urological Surgery (Surgical Amphitheatre)
	Lunch	Lunch	Lunch
Opening Meeting (The Lyric) Addresses: Dr. W. H. Welch presiding Sir Wm. Osler Dr. H. M. Hurd Miss M. A. Nutting	2.30 Pediatric Wards Dr. Howland 3.30 Dedication Hewetson Medallion 4.30 Herter Lecture 5 Ladies' Garden Party	3.30 Dedication of the J. B. Brady Urological Clinic Dr. W. H. Smith presiding Pres. F. J. Goodnow Dr. H. H. Young and other speakers	4.30 Herter Lecture
5 Garden Party Johns Hopkins Hospital Lawn			
Dinners Johns Hopkins Hospital Alumni Nurses	Dinner Alumni of Medical School	Dinner to Mr. J. B. Brady, Donor of the new Urological Clinic Class Dinners	Class Dinners

THE HERTER LECTURES FOR 1914.

The Herter Lectures will be given in connection with the Quarter Centennial Anniversary of the Opening of The Johns Hospital and the Twenty-first Anniversary of the Opening of the Medical Department of The Johns Hopkins University, upon Tuesday, Thursday and Friday, October 6, 8 and 9, 1914, at the Physiological Lecture Room, Monument and Washington Streets, at 4.30 p. m., by Thomas Lewis, M. D., University College, London, England.

Dr. Thomas Lewis in charge of the heart station at University College, and Editor of *Heart* has done important work in the study of cardiac conditions, and will present three lectures on the scientific study of the heart and its bearing on clinical medicine. He is the first clinical investigator who has filled the position of Herter Lecturer. The titles of his lectures will be announced later.

N.H.L.

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BULLETIN

OF

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THE SIGNIFICANCE OF THE THYMUS GLAND IN GRAVES' DISEASE.

By WILLIAM STEWART HALSTED, M. D., Baltimore.

It was perhaps in 1849 that the first experimental proof was brought of the action which a ductless gland might exercise upon the organism. Berthold, professor in Göttingen, transplanted the testicles of young cocks and noted that the birds so treated developed the masculine voice, sexual desire, comb and love of combat. He thus in considerable measure anticipated Brown Sequard, to whom the doctrine of internal secretions is generally accredited and who twenty years after Berthold, committed himself to the view that a gland, whether possessed of ducts or not, elaborated substances which were essential to the growth and maintenance of the body and for the preservation of health. It was a memorable meeting of the Société de Biologie of Paris at which, two decades after his first pronouncement, this supergifted man related in support of his views the results of experiments made upon himself. He testified, as you recall, that following the injection of testicular juice he observed an astonishing revivification of his physical and mental powers.

One of the least understood and most complicated of the various distinct but intimately associated mechanisms at work in sustaining the orderly activity of the animal body is what has been termed the chemical correlation. Each organ, each tissue and each cell of the organism may exert a chemical influence upon some other far removed tissue of the body and thus aid in bringing about the adaptations and readjustments essential for the integrity and life of the whole.

The acid chyme passing into the duodenum stimulates the epithelial cells of the mucosa to the production of a substance which by way of the blood stream calls forth responses in pancreas, intestines and liver, exciting the secretion of pancreatic and intestinal juices and of bile. Bayliss and Starling proposed the name Hormones (*ὁρμαῖω*, to awaken, stir up) for such physiological products as serve to arouse the various organs to activity.

The structures which produce Hormones are commonly called endocrine (*κρινεῖν*, to separate) organs or glands of internal secretion.

Meltzer believes that, strictly speaking, such products of the chemical action of organs as must be regarded as terminal resultants of the decomposition processes, as the waste or by-products of metamorphosis, products which enter the circulation merely for the purpose of prompt elimination, should be differentiated from those substances which, formed in specific manner in individual or special organs, are taken up by the circulation and carried to distant parts, there to fulfil particular functions. Only these latter substances should, in the opinion of Meltzer, Gley and others properly be designated as Hormones, and Gley has proposed the appellation Parhormone for the decomposition products which invariably result from cellular activity and which as irritants might exercise a deleterious influence did not the fluids and tissues of the body form definite protective reactions.

Hormones can in two ways exercise their functions either by direct action upon the tissues or by means of the nervous system. In addition to these relatively direct methods of manifesting their action upon the terminal apparatus it is quite certain that the secretion of a given gland may act indirectly or through the agency of other hormonopoetic organs. For example, the influence of the thyroid by way of the thymus upon the activities of the stomach. To what extent the visceral nervous system plays a part and what may be the sequence of events in the course of the complicated interaction of the endocrine glands may in a measure be determined by experimental studies in metabolism. Thus it has been ascertained that in animals the glycosuria which develops on administration of adrenalin vanishes after excision of the thyroids. If these animals are now fed with thyroid extract the glycosuria reappears. On the other hand, in the pancreatectomized animals excision of the thyroid does not cause the glycosuria to disappear.

Studies in metabolism have taught us that the thyroid and pancreas on the one hand and the pancreas and chromofine system on the other reciprocally inhibit. Between the thyroid and chromofine system, however, there exists a reciprocal potentiation. Hence when hyperthyroidism gives rise to glycosuria it may conceivably do so by inhibiting the pancreas. In a still more roundabout way the thymus via thyroid, via pancreas might possibly bring about glycosuria unless, perhaps, the influence of the thymus upon the adrenals were protective.

Modern pharmacology regards as antagonists the sympathetic and autonomic* nervous system. As the sympathetic system possesses in adrenalin a specific pharmacological stimulant so analogously the autonomic system has in pilocarpin and muscarin its specific irritants. One can by the administration of thyroid extract produce symptoms in animals and man which strikingly resemble the stimulating effects of pilocarpin or muscarin (sweating, diarrhoea, disturbances in respiration, lymphocytosis, eosinophilia, etc.).

The standpoint has accordingly been taken that in the thyroid there is a constituent which produces an effect similar to that of the poisons of the pilocarpin group. In favor of this view speaks, especially, the well-known antagonism between thyroid extracts and atropin, which is an antidote for pilocarpin and muscarin. It has now been attempted on the basis of these physiological facts, which indicate that from the thyroid gland impulses may be sent out along the tracts of the sympathetic as well as the autonomic system, to distinguish the symptoms of Graves' disease which might be due to irritation of the sympathetic from those which might be attributed to autonomic stimulation. (Eppinger).

SYMPATHETICO-TONIC BASEDOW SYMPTOMS.

1. Pronounced protrusio bulbi.
2. Von Graefe, absent.
3. Löwi's phenomenon, positive.
4. Möbius, positive.
5. Dry bulbs.

* This word is used in the restricted sense, and not as intended by Langley who proposed the term *autonomic* for the entire sympathetic system.

6. Greatly increased activity of the heart with less pronounced subjective disturbances.

7. Sweating and diarrhoea, absent.
8. Falling out of hair.
9. Eosinophilia, absent.
10. Inclination to fever.
11. Alimentary glycosuria.
12. Refractory behavior to pilocarpin.

VAGO-TONIC SYMPTOMS.

1. Relatively moderate degree of tachycardia.
2. Pronounced subjective heart symptoms.
3. Von Graefe, definite.
4. Wide lid-clefts.
5. Möbius, absent.
6. Slight protrusio bulbi.
7. Increased lachrymation.
8. Profuse sweating.
9. Diarrhoea.
10. Disturbances of digestion.
11. Eosinophilia, likely.
12. Alimentary glycosuria, absent.
13. No adrenalin-glycosuria.
14. Pigmentation.

There are certain exceptional, more or less sharply differentiated cases of Graves' disease which every physician and surgeon who has actively interested himself in the subject must vividly recall. During the past twenty-three years in a series of about 500 I have seen perhaps twenty which were especially typical of their kind. The characteristic features which most of them presented were great emaciation, dilatation of the heart, sweating, diarrhoea, relatively slight exophthalmus, not excessive tachycardia, small goitre, and frequently a peculiar greyish bronze-hued skin.

Confronted with a case of this kind, I have repeatedly said to my assistants:

Here is another of these puzzling, dreadful cases. The patient is not highly thyrotoxic; the thyroid is hard, not large, nor pronouncedly vascular; if a lobectomy is performed she may die, but probably not with the stormy symptoms which suggest extreme thyroid intoxication. If death occurs it may be sudden, possibly not until several days after the operation, and perhaps when the patient seems to be convalescing.

In one of these cases death occurred four days after the ligation of a single artery under local anaesthesia. The operation, including the injection of the local anaesthetic and the sewing up of the tiny wound, required exactly ten minutes. One night, as I have said, four days after the operation, and a few minutes after the nurse had charted the pulse as 90, the patient awoke with a start, sat upright in bed, gasped for breath and died. The following case died suddenly about 30 hours after a thyroid lobectomy when we had ceased to be apprehensive about her:

CASE I.—A. V. C. (No. 33,010). Aet. 47. Admitted October 8, 1913. Except for whooping cough at the age of 15, mumps at 19 and measles at 21, patient states that she has enjoyed good health until about 4 years ago.

In January, 1909, patient experienced on swallowing the sensation of a "lump in her throat." At about the same time she was seized with a severe headache, became very nervous, suffered from palpitation and vomited several times. Thinks she had fever in this attack. Almost immediately the thyroid gland "began to swell." She was quite ill for 3 or 4 months but in May of the same year felt as well as ever. Her recovery was so complete that she considered herself in normal health until January, 1913, when she was taken ill again quite suddenly with precisely the same symptoms as in the previous attack. Palpitation and shortness of breath were more pronounced than at first; diarrhœa, vomiting and difficulty in swallowing also became troublesome symptoms. Cessation of the menses occurred about that time. Since July 1, 1913, she has been confined to bed.

Examination.—Patient is greatly emaciated (weight 67 lbs.); is very nervous, constantly jerking about and tossing her head; there is fine tremor of the fingers and tongue. She has decided mental aberration, ideas of persecution and grandeur; has bad dreams; talks to angels; is confident that her mind is affected, etc. Has staring expression; is very nervous; the whole body seems to be shaken by the heart-beat. The skin is ashy-bronze in hue. There is slight exophthalmus; definite von Graefe; convergence fair; rather wide palpebral clefts, but sclera covered. Joffroy sign absent; pupils react to light and accommodation. The hair is dry, grey, thin and falling out. Thyroid uniformly and moderately enlarged and very firm. Faint bruit but no thrill over thyroid arteries. No palpable enlargement of any lymphatic glands. The carotids throb forcibly. Veins of neck pulsate. There is great emaciation; deep supra- and subclavicular fossæ. Movements of respiration symmetrical. Lungs clear. Respiration 28. Thymus: there is no definite retro-manubrial dullness; X-ray negative. The heart is greatly dilated. There is a soft blowing systolic murmur over the whole cardiac area; it is heard best at apex. Pulse 140 to 155 and over per minute, and irregular. Arteries not hardened, blood pressure 115 to 125. Abdomen scaphoid. Marked aortic pulsation. Edge of liver not palpable.

Blood.—White corpuscles, 13,360; red, 4,404,000; hæmoglobin 61 per cent.

October 13, 1913. *Differential Blood Count.* 250 cells counted.

	Cells	Percent-age	Actual number of each in cmm.
Polymorphonuclear neutrophiles	128	51.2	6840
Small mononuclears	86	34.4	4595
Large mononuclears	21	8.4	1222
Transitionals	5	2.0	267
Eosinophiles	3	1.2	160
Basophiles	1	.4	64
Unclassified	7	2.8	374
Myelocytes	2	.8	106

October 20, 1913. Patient vomited frequently until five days ago. Has two to three or more watery stools a day. Has persistent cough.

October 21, 1913. *Operation I. Ligation of Left Inferior Thyroid Artery.* The artery was easily found and tied. It was as large as a vertebral artery. Patient's pulse rose to 200 and over during the operation under novocain, nitrous oxide gas, and a few drops of ether.

October 24, 1913. Patient remarkably improved since the operation. Restlessness greatly relieved. Vomiting has ceased. Pulse now averages only 100.

October 25, 1913. *Operation II. Gas. Ligation of Right Inferior Thyroid Artery.* Artery very large, very thin-walled and blue like a vein. Operation required only a few minutes.

October 30, 1913. Patient has improved rapidly since second operation. Is quite cheerful. Hair regaining lustre.

October 30, 1913. *Differential Blood Count.* 250 cells counted. White blood cells 8300.

	Cells	Percent-age	Actual number of each in cmm.
Polymorphonuclear neutrophiles	122	48.8	3984
Large mononuclears	37	14.8	121
Small mononuclears	69	27.6	2201
Transitionals	21	8.4	704
Eosinophiles	1	.4	41

November 4, 1913. Marked improvement in patient's general condition. Pulse 88. Patient eats heartily; neither vomiting nor nausea.

November 11, 1913. No pronounced change in patient's condition during the past week. Appetite large but there has been no gain in weight (60 lbs.).

November 16, 1913. Patient has gained 4¾ lbs. in past five days.

November 24, 1913. No definite improvement during past week.

November 25, 1913. *Operation III. Right Lobectomy.* Gas and a few drops of ether. Operation simple and rapid. Patient's pulse rose only occasionally to 180, but was usually about 160 during the operation. At the first operation it rose to 200 and over. At the end of the operation the patient's condition was excellent.

November 26, 1913. *Differential Blood Count.* 250 cells counted. White blood cells 18,400.

	Cells	Percent-age	Actual number of each in cmm.
Polymorphonuclears	155	62.0	11,408.0
Small mononuclears	51	20.4	3,753.6
Large mononuclears	22	8.8	1,619.2
Transitionals	8	3.2	588.8
Eosinophiles	5	2.0	368.0
Basophiles	5	2.0	368.0
Unidentified	4	1.6	294.4

November 26, 1913. Patient had a fairly comfortable night and seemed to be convalescing satisfactorily until 1.20 p. m. to-day when she was found sitting up cyanotic and gasping for breath, coughing, trying to clear her throat, excited and apprehensive. Pulse very irregular. Respirations 40 to 50. Area of precordial dullness markedly increased, extending 4 cm. to the right and 10 cm. to the left of the median line. At 1.50 p. m. she became quiet, seemed fairly comfortable and dozed. Pulse 140 to 180 and irregular in force and rhythm. Cyanosis less.

3.40 p. m. Suddenly seized with another dyspnœic attack. Respirations became more labored and at 4.05 p. m. ceased. The heart apparently stopped beating about one minute before the cessation of respiration. The temperature rose to 101.5° F.

Autopsy. (Dr. Reid.) Subject strikingly emaciated. Left lobe of thyroid slightly enlarged; small slice of right lobe in region of the parathyroids. Cardiac dilatation. Emphysema of both lungs; broncho-pneumonia. Large thymus extending down to the auricles. Fatty degeneration and atrophy of liver; small adenoma of liver. Mesenteric glands rather larger than normal; otherwise no enlargement elsewhere of the lymphatic glands. Dilated, atrophic stomach. The thymus gland was thick but not broad enough to cast an X-ray shadow beyond the manubrium, It was triangular in shape, the finely tapered apex reaching to the top of the manubrium, the broad base extending to and partly covering the auricles of the heart.

The endocrine glands have been carefully studied microscopically and will probably be reported upon at other times by the various men to whom these organs were specially entrusted. I was particularly interested to find that in the thyroid glands the follicles instead of showing the usual picture found in exophthalmic goitre were for the most part circular and distended with densely staining colloid without vacuolation. The epithelial cells were low-cuboidal or flat. In places,

however, throughout the gland the colloid was rarefied and the cells high.

In this patient the vago-tonic symptoms predominated (diarrhœa, vomiting, small goitre, slight exophthalmus, definite von Graefe, Möbius not pronounced, intense subjective symptoms, pigmentation).

Was this a case of thymus death?

Physiologists, pharmacologists, pathologists and clinicians are rapidly reflecting, consciously and unconsciously, helpful light for the interpretation of the clinical phenomena and dire results in cases belonging more or less definitely to this category.

In 1910 Meltzer* made the following cautious statement concerning the thymus gland:

With our present knowledge of the importance of the other ductless glands we are hardly justified in assuming that the thymus is a worthless fetal remnant. But we have to acknowledge that as yet there are no reliable observations or experiments which indicate clearly that the thymus has a function in post-uterine life.

Von Mikulicz (1895) called attention to the occurrence of enlarged thymus in severe cases of exophthalmic goitre, and Rehn (1899) suggested that it might be well to attack the thymus gland surgically in this disease. In 1908 Hart expressed the opinion that abnormal activity of the thymus gland might produce the clinical picture of Graves' disease.

It was my good fortune to be present when Garrè, at the 40th Congress of the Deutsche Gesellschaft für Chirurgie (1911) took part in the discussion of Kocher's paper on exophthalmic goitre in order to report the first instance in which the thymus had been primarily removed for the cure of this disease. Although well aware of the fact that a "persistent" or revived thymus had repeatedly been observed in "Basedow" he was astonished to learn from the statistics obtained by his assistant, Dr. Capelle, that a thymus persistens hyperplastica had been found in 95 per cent of the fatal cases, whether death was due simply to the severity of the disease, or occurred during the operation, or within twenty-four hours after the strumectomy.

So impressed was Garrè with these findings that he finally determined to test the effect of thymectomy in cases in which there was good reason to believe that the thymus was enlarged. It seemed to him that a severe and florid example of Basedow should be selected for the experiment and that the thyroid gland should be unmolested in the operation, the purpose of which was to determine the effect of a thymectomy upon the symptoms of the disease.

The result in his first case was as follows:

Clinically no definite influence on the struma, the exophthalmus or the eye symptoms, but an unequivocal improvement in the general condition as expressed by the "éclatant" quieting of the heart's action, rapid increase in weight, and a complete regression of the Kocher blood-picture, the lymphocytes falling from 40 to 25 and then to 10 per cent.

* Meltzer. Animal Experimentation in Relation to Our Knowledge of Secretions, Especially Internal Secretions. Proc. of the Path. Soc. of Phila., Sept., 1910.

In his second case Garrè performed simultaneously a hemistrumectomy and thymectomy.

The striking results which followed the first of these operations forced upon him the thought that the hyperplastic thymus in exophthalmic goitre displays an action essentially similar to that of the thyroid and that the thymus persistens aggravates the symptoms of the disease.

Professor Garrè gave to his assistant, Dr. Capelle, credit for the work and the thought which led them both to these conditions, which he said finds essential support in the proof by Klose that in the thymus-substance there is a heart-poison. Aside from the special action of the thymus there exist certainly, said Garrè, important reciprocal relations between these two glands, and for the following reasons:

1. After thymus extirpation, the blood-picture, which, by Kocher, is considered characteristic of Graves' disease, returned to normal precisely as after a successful strumectomy.

2. His assistant, Dr. Bayer, had recently demonstrated that intraperitoneal injections of the expressed juices of the thyroid as well as of the thymus produce the Kocher blood-picture, whereas the juices of colloid struma and of normal thymus influence the blood-picture to a much less extent.

3. They found in a thyroid gland which had been removed six months after a thymectomy microscopical evidence of regressive changes.

4. Gebele had announced at the previous Congress that the prompt implantation of normal thymus in thyroidectomized dogs prevented the appearance of cachexia strumipriva.

5. He was able to state, thanks to the permission of Dr. Bircher, that the latter had twice produced the typical Basedow picture by the intraperitoneal implantation of the fresh, pathologically hyperplastic thymus. These and other facts made him unable to subscribe to the generally accepted view of Möbius that the thyroid is alone responsible for the disease. On the other hand he was not prepared to take the extreme view of Hart that there was a purely thymogenic form of Basedow.

I have presented in such detail the views so briefly and cautiously expressed in 1911 by the highly gifted director of the surgical clinic in Bonn because this contribution of Garrè and Capelle marks an epoch in the developing story of Graves' disease and its treatment, the importance of which is as yet not realized.

During the past three years the research work on the thymus, which already had been considerable, has assumed great proportions, and for surgeons interested in Graves' disease this gland has become a theme on which their attention may well be focused.

And now, just a few weeks ago, appears a most convincing paper by von Haberer, the youngest of Billroth's assistants, and, until his promotion to the directorship of the Innsbruck surgical clinic, first assistant to von Eiselsberg in Vienna, who is also a distinguished product of the school of Billroth. The results of thymectomy in von Haberer's case, number 3, are so remarkable as to be almost unbelievable were they recounted by an authority less eminent and trustworthy.

CASE 3.—Von Haberer.* Merchant, æt. 30; in his earlier years athletic; of late overworked in his business, but well until the autumn of 1909, when after an attack of fever, he noticed a marked increase in the frequency of his pulse, loss of zeal for work and a feeling of general bodily discomfort. About six months later he observed that his eyes were abnormally prominent, that he was becoming nervous and tremulous and subject to attacks of profuse sweating, and that he experienced feelings of cold in the legs. The greatly increased and irregular action of his heart caused him especial uneasiness. In the spring of 1911 a part of the thyroid gland was removed, and thereafter, for a time, his symptoms, the tachycardia excepted, were somewhat relieved. In the winter of 1911, after unusual business stress, the heart symptoms became greatly intensified and hæmoptysis and dyspnœa supervened. The dyspnœa became so great that the patient was apprehensive at times lest he choke to death. He sought relief at the hands of Prof. Kocher in Berne, who ligated the thyroid arteries of the unremoved lobe. No relief was obtained from the arterial ligation, on the contrary the patient's condition became alarmingly worse. He frequently had attacks in which a bloody froth was expectorated and consciousness lost. He finally could not walk without provoking these attacks.

On the seventh of December, 1912, the patient presented himself at the clinic in Innsbruck of von Haberer. He was cyanotic, gasping for breath and covered with cold sweat; the pulse could not be felt in the peripheral arteries. Fearing that the man might die in his office, Prof. von Haberer had him hastily despatched to a sanatorium. After a short rest in bed in a half sitting posture (the only one endurable for the patient) the pulse returned at the wrist. It was 160, very irregular and unequal. Exophthalmus was particularly pronounced on the right side; skin and mucous membranes cyanosed; slight von Graefe and Möbius signs on both sides; tremor and great dyspnœa; right lobe of thyroid very slightly enlarged; left lobe not palpable. Over both lungs signs of œdema and congestion-bronchitis; heart much enlarged, extending on the left side, four finger-breadths outside of the mammary line. Liver greatly increased in size, its lower thick border extending as low as the navel. Slight but definite icterus. Compression of the trachea by the thymus was excluded both by percussion and the Roentgen ray. There was, however, behind the manubrium a triangular shadow which, without demarcation, blended with the shadow of the heart. Percussion revealed no unusual dullness.

The patient begged piteously for operation, indifferent to its dangers; desirous only to be relieved of his great distress. Prof. von Haberer refused to interfere surgically, being convinced that if an operation were undertaken at that time it would result fatally. The physician called in consultation agreed that the patient's condition was hopeless, the heart being exhausted. The thyroid symptoms he regarded as a complication of relatively minor importance and believed that medication would accomplish nothing for the heart. The patient was kept in bed and treated with diuretin and digotoxin. In the course of ten days the condition of the lungs was somewhat improved, but the pulse, never dropping below 140, remained irregular with frequent periods of galloping rhythm. The differential blood count gave polynuclears 57 per cent; small lymphocytes 27.6 per cent; large lymphocytes, mononuclears and transitionals 12.3 per cent; eosinophiles 2.9 per cent; mast cells 0.2 per cent; coagulation was slightly delayed.

December 19, 1912. All were still agreed, and the patient assured, that he could not survive an operation of any sort. Nevertheless, von Haberer, having in mind the somewhat analogous case of Garré's finally decided to yield to the patient's entreaties, and on

December 19, under local anæsthesia, succeeded after prolonged search in extracting from behind the manubrium a piece of tissue 3 cm. long and $\frac{1}{2}$ cm. thick, which resembled fat and macroscopically seemed to contain no thymus gland. Greatly disappointed at the result of the operation and believing that the last hope for the patient had vanished, von Haberer closed the wound. Towards evening of the same day the patient announced that he felt much better and that his dyspnœa had disappeared. On the fourth day after the operation he became much worse; the pulse was feebler and more frequent, the liver increased in size and the icterus deepened. The following morning, however, and each day thereafter improvement was noted, and on the third of January, 1913, two weeks after the operation, the patient was discharged from the hospital. Three months later (April, 1913) he returned for examination. The surgeons and physicians were astonished at the result. The apex beat was in the mammary line, the pulse 84, although still irregular, the cyanosis and icterus had disappeared; the liver was of normal size, and the color of the skin was good and fresh. The subjective condition was as satisfactory as the objective. The patient declared that he felt perfectly well; he could work as tirelessly as ever and could even climb mountains. In September of the same year this patient wrote that he had climbed for sport a mountain over 7500 feet high.

Three primary thymectomies have been reported, all of them from Garré's clinic. To these may, however, be added Sauerbruch's case in which only the ligation of one superior thyroid artery preceded the operation on the thymus. In all of these cases the effect of the operation upon the general condition of the patient and upon the blood-picture was unequivocally beneficial. Of the combined operation, thyroidectomy plus thymectomy, eight cases have been reported by von Haberer; and Capelle and Bayer state that several times in the clinic of Garré this operation has been performed.

Klose states in his recent book on the thymus gland that he has in five cases of Basedow's disease resected the thymus. In each instance there was striking improvement in the patient's general condition and return of the blood-picture to the normal. I have excised a small portion of the thymus with one lobe of the thyroid in two cases of which I shall speak later.

It has been our practice of late in the strumectomy operations to investigate the contents of the space between the trachea and the manubrium with the object of determining the possible presence of an enlarged thymus, and in a few instances we have made a fairly thorough search for this gland. Only twice have we found it enlarged; in both instances we should have been disappointed had there been no traces of thymus and our faith in some of the most important strands of the complicated web which the pharmacologists, the physiologists and the clinicians are weaving to represent the interdependent activities of the endocrine glands would have been shaken.

CASE 2.—H. P. (Sur. No. 31,648). Æt. 13. Admitted to the Hospital March 6, 1913.

Complaints of difficulty in breathing, "feeling lazy," and inability to work. During the past four or five years he has had attacks of vertigo, occasionally with loss of consciousness; also attacks of nausea and vomiting preceded usually by headache. Patient might remain in bed for a week after such attacks.

Patient believes that his present illness began two years ago. He noticed first a swelling in the neck which has gradually in-

* Mitteilungen aus den Grenzgebieten der Med. u. Chir., Bd. XXVII, Heft 2, p. 210.

creased in size; then began to have shortness of breath and the sensation of pressure on the trachea. He could not read aloud for any length of time. He could not run or ascend stairs quickly. During the past five months he has had dyspnea on lying down and has been unable to sleep on less than three pillows. Ambition for work and play is lost. He is unable to talk loud and finds it impossible to shout. Has a hoarse cough and desire to clear the throat. For the past four or five months he has experienced some difficulty in the swallowing of solid foods, and at times even of liquids; his bowels are evacuated four or five times a day. He has occasional attacks of vomiting before breakfast. Has become irritable. Has not observed palpitation of the heart. Does not perspire excessively.

Physical Examination.—Boy is well nourished and well developed. The hair is oily; the skin neither abnormally dry nor abnormally moist. There is no exophthalmus; the von Graefe sign is positive at times; the other eye-signs are absent. The thyroid gland is enlarged to perhaps three or four times its normal size. There is definite retro-manubrial dullness. The X-ray shows a suggestive shadow. A soft systolic bruit is heard over a very slightly enlarged heart. The pulse is regular, 80 beats per minute. Tremor absent. Cervical, inguinal, submaxillary and axillary glands are palpable.

March 7, 1913. *Differential Blood Count.* 300 cells counted.

	Cells	Percentage
Polymorphonuclear neutrophiles	160	53.3
Small mononuclears	102	34.0
Large mononuclears	23	7.6
Transitionals	8	2.7
Eosinophiles	3	1.0
Basophiles	2	0.7
Unclassified	2	0.7

March 18, 1913. *Operation. Excision of Right Lobe and Isthmus of Thyroid and a Small Piece of Thymus.*

March 26, 1913. *Differential Blood Count.*

	Cells	Percentage
Polymorphonuclear neutrophiles	183	61.0
Small mononuclears	86	28.6
Large mononuclears	15	5.0
Transitionals	7	2.33
Eosinophiles	2	.6+
Basophiles	2	.6+
Unclassified	5	1.6

December 11, 1913. (9 months after operation.) *Differential Blood Count.*

	Per Cent
Polymorphonuclears	68.0
Small mononuclears	23.0
Large mononuclears	5.0
Transitionals	3.0
Eosinophiles	1.0

February, 1914. *Examination.* The boy's health is almost restored. He is able to do a full day's work but is rather more fatigued by it than are other boys of the same age. He can sleep on one pillow and has had no attacks of vertigo, nausea or vomiting since the operation. The cough and difficulty in swallowing have disappeared. The diarrhoea has ceased.

As the operation in this case was a combined one, the great improvement which followed it cannot definitely be attributed to resection of the gland alone. The portion of thymus resected was, however, so small that I am inclined to believe that the strumectomy rather than the thymectomy was chiefly responsible for the good result.

CASE 3.—G. B. (No. 94,086). Aet. 12 years. Admitted to the hospital February 12, 1914.

Has had most of the infectious diseases of childhood (whooping cough, measles, scarlet fever, chickenpox, mumps), all before she was 7 years old. Occasionally has sore throat but has never had a definite attack of tonsillitis. Function of eyes and ears normal. Has always been a nervous child with poor appetite. Digestion apparently good, although she has each year two or three "bilious attacks" with nausea and vomiting. For the past five years the mother has had difficulty in fitting the collars of her child's dresses, but not until a few months ago did she notice that the neck was enlarged. The eyes have always been prominent, protruding at times more than at others. For the past 3 or 4 years the child has complained of a feeling of fullness in the neck, especially when tired and nervous.

Examination. A rather pale, sallow-looking, frail girl. Expression alert and intelligent. She is unusually clever in conversation. Not obviously nervous at present. Hair normally lustrous. Hands and feet warm and rather moist. No pigmentation of skin. Dermatographia. No dilatation of superficial vessels of forehead or temples. Possibly slight fullness of veins of upper eyelids. Eyes decidedly prominent. Sclera well covered by lids. Palpebral clefts 1 cm. A suggestive stare. Von Graefe doubtful. No other eye-signs. Pupils react to light and accommodation. Slight tremor of tongue, none of fingers. Pulse regular; 100 beats per minute. Accentuated throbbing of the carotids, particularly of the right carotid. Dilatation of superficial veins of neck on both sides. Neck enlarged; rather more so on the right than on the left side. Both lobes of thyroid palpable, the right more definitely than the left. The isthmus is prominent and measures 2.5 cm. vertically. There is neither bruit nor thrill in the gland. Circumference of neck over the isthmus is 28 cm. The entire gland seems of normal or rather soft consistence. There is a suspicion of retro-manubrial dullness. The X-ray reveals, however, no shadow suggestive of the thymus gland.

Tonsils markedly enlarged; crypts visible. Posterior cervical and axillary glands are palpable. Finger tips are slightly clubbed. Child complains of palpitation of the heart and shortness of breath on exertion. States that on two or three occasions she has been obliged at night to sit upright in bed to relieve a feeling of slight suffocation. Has usually two and sometimes three stools a day. Has never been constipated.

February 12, 1914. *Differential Blood Count.* White blood cells 7000. Hæmoglobin 92 per cent.

	Cells	Percentage
Polymorphonuclear neutrophiles	120	60.0
Small mononuclears	71	35.5
Large mononuclears	5	2.5
Transitionals	3	1.5
Eosinophiles	1	.5

February 19, 1914. *Operation. Resected Right Lobe of Thyroid and a Small Piece of Thymus Gland.* The right lobe of the thyroid, about 2½ times the normal size, was resected according to our regular method, a portion of the posterior part being left to protect the parathyroids and the recurrent laryngeal nerve.

The thymus gland was found to extend upwards almost to the inferior pole of the right lobe of the thyroid. The piece of the thymus resected was hardly larger than the child's little finger.

February 21, 1914. (2 days after operation.) *Differential Blood Count.*

	Cells	Percentage
Polymorphonuclear neutrophiles	154	77.0
Small mononuclears	25	12.5
Large mononuclears	11	5.5
Transitionals	10	5.0

It is interesting to note the fall in mononucleosis. Nine days before the operation the percentage of mononuclears was 38; two days after the operation it had fallen to 18. The

child and mother are greatly pleased with the general improvement which they think has taken place since the operation. It is too soon for us to judge of this.

It is the belief of the few who have expressed an opinion on the subject that the overactivity of the thymus manifests itself chiefly or only after the hyperthyroidism has existed for some time—that it is not observed in the early stage of the disease.

In my patients 2 and 3 the thymus symptoms predominated (attacks of dyspnoea, diarrhoea, no tachycardia, not much enlargement of the thyroid and not very definite eye symptoms).

So one cannot but feel that the hyperthymusism may have been primary in these cases and that later on the thyroid symptoms might have predominated. We shall try to follow carefully the subsequent history of these children; and as only a part of one lobe of the thyroid and a very small portion of the thymus of each child was removed we may not have influenced profoundly the natural development of the disease.

A case upon which a double thyroid lobectomy was done two years ago returned recently for examination. The thymus being still enlarged it was treated for four hours by the emanations of 1300 milligrams of radium applied over 16 squares. Although there has been after 10 days no reduction in the size or density of the X-ray shadow, two thyroid nodules, as large as filberts, hypertrophied remnants of isthmus, entirely disappeared within 24 hours. Dr. Burnam, who applied the radium at Dr. Kelly's Sanatorium, believes that the thyroid nodules vanished because of the inhibited activity of the thymus. He thinks it is exceedingly unlikely that the emanations could have directly affected the thyroid.

The results of the combined operations have been, without exception, remarkably good; unmistakably better, I should say, than we ordinarily obtain from the operation upon the thyroid gland alone. Particularly striking has been the relative absence of the reaction which is usually observed in the 36 or 48 hours following thyroid lobectomy. The post-operative course in the experience of von Haberer could not be distinguished from that observed after operations for ordinary struma. This seems the more remarkable because in all these cases there was the complication of an enlarged and persistent thymus. The improvement was immediate and so strikingly pronounced that I agree with von Haberer in believing that it must be attributed to something more than mere accident.

That the thymus plays an important part in Graves' disease has, I think, been demonstrated beyond question by the results which have followed thymectomy. That some sort of relation exists between the two organs we have further evidence from the physical examination of the non-fatal cases, from the autopsy table, and from experiments on animals.

Palpation just above the manubrium, particularly pressure downwards towards the mediastinum, and over extension of the head, may be complained of by patients with persistent thymus on account of the shortness of breath occasioned by these maneuvers. The Roentgen-ray and the percussion-note over the area occupied by the thymus may give useful information; but the absence of both dullness and shadow does not

exclude the presence of a persistent gland, nor do we know as yet how small a thymus may be responsible for symptoms.

It has been estimated as a result of non-operative clinical examination that in about 40 per cent of all cases of exophthalmic goitre the thymus is persistent. The actual percentage it remains possibly for the surgeon to determine by systematic exploration. We have, I think, no absolute evidence that the thymus may be completely wanting in a case of Graves' disease; and since, as I have stated, we do not know how small a fragment of this gland may suffice to play a part in the disease, we are not as yet in a position to assert that exophthalmic goitre may exist entirely uninfluenced by the thymus. Von Haberer, however, reports an outspoken case in which careful operative search failed to reveal its presence.

Enlarged thymus not infrequently accompanies colloid goitre. Attention was called by Astley Cooper and by Virchow to this association. The question naturally suggests itself, has the persistent thymus the same significance in both these forms of goitre, one of which we hold accountable for symptoms of hyperthyroidism, whereas with the other the picture of underactivity of the thyroid is associated? Is it not conceivable that the persistent thymus in colloid goitre may in some cases represent responses from time to time to periods of perhaps overlooked, hyperfunction of the thyroid, and if so that indeed for the "Kropfherz," a contributing factor may be found in the thymus?

From the post-mortem examination of cases of exophthalmic goitre which have died of intercurrent disease it has been ascertained that the thymus gland is persistent in about 82 per cent of them; and in those cases which have died of heart failure after operation enlargement has been found, as already stated, in about 95 per cent. Probably it will be ascertained that the percentage has been underestimated for the reason that enlargement of the thymus may not hitherto have been so completely noted or looked for as it will be in the future. Then, too, we must bear in mind the important lesson taught us from von Haberer's Case No. 3, that the severest thymotoxic symptoms may be caused by fragments of thymus so small as to be unrecognizable as such by the naked eye.

At the Johns Hopkins Hospital there has been only one opportunity to make an autopsy on a case of Graves' disease which died after operation. In this instance, as I have mentioned, a long, thick thymus gland was found tapering out from near the top of the manubrium sterni to the auricles of the heart.

What are the particular symptoms of Graves' disease which indicate a preponderate influence of the thymus? Eppinger, Garré, von Haberer, Kloss, Capelle, Bayer, van Noorden, Jr., and indeed almost every clinician who has familiarized himself with the literature would say it is the vago-tonic symptoms. But do we know quite definitely what the vago-tonic symptoms are? And in case they should be determined shall we be in a position to assert that the thymus is or is not alone responsible for them?

Naturally it will fall to the lot of the surgeon to discover which of the symptoms are dissipated by the removal of the

thymus; but even when this has been ascertained the proof is not furnished that no other organ could have had a part directly or indirectly in their causation.

Let us consider, for example, the protrusion of the eyeball, a symptom which according to MacCallum and others may be caused by stimulation of the sympathetic. If it is true that this is a sympathico-tonic symptom and if the thymus were activated solely by the autonomic system, the excision of this gland might not be expected to affect directly and promptly the exophthalmus. But as a matter of fact recession of the eyeball in at least one of von Haberer's cases was much more prompt than has perhaps ever been observed after strumectomy alone. The effect on the thyroid gland, particularly as to its vascularity, seems to have been quite as striking in von Haberer's experience; it must, however, be remembered that except in one case the combined operation was performed.

To discuss the grounds on which the various signs have been assigned to their special groups would carry us beyond the purpose of this paper. I might say, however, by way of illustration, a word with reference to the incomplete convergence of the eyes. This, the Möbius sign, is assigned to the sympathico-tonic group. It was explained by the late Dr. Landström and his supporters as due to the contraction of the Müller-Landström muscle of the orbit which is supposed to be responsible for the protrusion of the eyeball and by the particular arrangement of its fibers to embarrass the action of the internal rectus. There are some, and especially certain countrymen of Landström, who do not consider the demonstration complete that the Müller-Landström muscle is responsible for the exophthalmus. Furthermore, as I have said, the eyeball may promptly recede after thymectomy, and with its recession the Möbius sign may vanish, which is contrary to what might have been expected of a sympathico-tonic symptom after the excision of an organ activated chiefly by the autonomic or vago-sympathetic system.

Surgeons the world over have learned from an experience which is now very large that the majority of patients afflicted with exophthalmic goitre may be relieved of their symptoms by strumectomy, but that in a certain percentage of the cases the cure may be incomplete even after resection of the greater part of both lobes of the thyroid gland (Halsted).

I have performed perhaps 650 operations upon about 500 patients with Graves' disease. A one-sided lobectomy, the operation ordinarily done, has resulted in an approximate cure in possibly 60 per cent of my cases, but in at least 25 per cent the patient has not been sufficiently relieved by a one-sided lobectomy to resume her full duties, and in certainly more than 60 per cent (possibly 70 or 80 per cent) there remain symptoms of overactivity of the thyroid or thymus or of both of these glands sufficiently pronounced to be detected by the expert clinician.

The results of my experience as regards the cure of Graves' disease by one-sided lobectomy are quite at variance with the views of other surgeons.

In some 47 cases in which the improvement was altogether unsatisfactory after the excision of one lobe the other was re-

RESULTS OF OPERATIONS FOR BASEDOW'S DISEASE.*

Year	Authors	No. of Cases	Cures	Considerable Improvement	Slight Improvement	No Improvement	Deaths
			%	%	%	%	%
1896	Schulz	20	90.0	5.0	5.0
1898	Wolf	9	66.5	22.5
	Helferich	6	66.6	16.7
1900	Reinbach (v. Mikulicz) .	18	66.5	22.5	5.5	5.5
1902	Witmer (Krönlein)	23	40.9	36.2	9.2	9.2	9.2
	Th. Kocher	59	76.0	14.0	3.3	6.7
1903	Curtis	11	60.0	10.0	30.0
1904	Mayo	40	67.5	17.5	15.0
1905	Lessing (König)	8	50.2	37.3	12.5
	Hartley	21	87.5	12.5
1906	K. Schulze (Riedel)	50	72.0	12.0	2.0	14.0
	A. Kocher	167	93.7	6.3
1907	Itzina (Hildebrand) ...	7	85.7	14.3
	Mayo (only new cases) .	136	78.2	19.6	2.2
1908	Landström	54	50.2	15.3	29.0	5.5
	Moses (Garrè)	28	16.9	41.6	24.9	12.5	4.1
1909	Klemm	32	93.2	3.4	3.4
	Th. Kocher	153	98.7	1.3
1909	MacCosh	22	14.5	72.7	8.2	4.6	4.6
	Hänel	21	38.1	42.8
1911	Sudeck	26	84.6	4.0	4.0
	Baruch	40	72.5	12.5	15.0	15.8
1912	v. Eiselsberg	44	61.4	34.1	4.0
	Enderlen	40	70.0	20.0	2.2	2.2
1912	Klose	61	75.5	9.8	1.6	13.1
	Weispfennig	30	60.0	6.6	23.3	10.0

*Klose, Die Basedowsche Krankheit. Erg. d. Inn. Med. u. Kinderheilk. Band X, 1913.

moved. Of particular interest to me has been the observation, which we have made several times, that definite improvement may not be observed until both lobes have been almost completely excised. In a number of cases—all of them severe—in which the preliminary ligation of three or four arteries plus a single lobectomy was followed by little or perhaps inappreciable benefit the symptoms vanished, almost magically, on the removal of the remaining lobe. I should explain, parenthetically, that I never excise the entire lobe; a small slice is always left posteriorly to protect the parathyroid glands, for the reason that the chances are considerable that the other side may have to be operated upon. It is undoubtedly because surgeons have so universally confined their operations to the excision of one lobe plus, perhaps, the ligation of an artery of the other, that the results have not been better than they are. And you will agree with me that it is rather absurd to conclude that if the excision of an arbitrary amount of a gland supposed to be chiefly responsible for the symptoms did not cure or relieve them it would be useless to remove more of the offending organ.

Now although all of the symptoms including the exophthalmus may be cured by strumectomy, the blood-picture may remain unchanged, at least for a considerable period. We have, for example, five cases in our wards at present whose mononucleosis is as great and in one of them greater than before operation. In one the four arteries have been tied and one lobe resected. In two both lobes have been excised, and in the fourth, a very serious case, the inferior arteries were first ligated, then the superior arteries; next the right lobe and then the left was resected. This patient's health has already been almost completely restored but the mononucleosis is 53

per cent (small mononuclears 34 per cent, large mononuclears 19 per cent), 4 per cent higher than on admission.*

Baruch, Sudeck, Klose, Melchoir, Lampé and Liesegang and others would seem to have brought proof from extensive clinical observations that the pathological blood changes in Basedow's disease remain uninfluenced by the excision of the thyroid gland.

Klose states it is universally conceded that all the symptoms of Graves' disease may disappear after thyroidectomy but that the disordered blood-picture is supposed to remain unchanged, and hence if we desire a hæmatological cure we must attack, surgically, the thymus. Another particular indication, according to Klose, for the excision or destruction of the thymus is the fact that in Graves' disease this gland is qualitatively and not merely quantitatively altered and may cause toxic as well as mechanical injury to the heart.

Borchardt a little more than a year ago reported † the result of his studies in the medical clinic of Lichtheim at Königsberg of the blood-picture in diseases of the endocrine glands. He examined 31 cases of Graves' disease, ten of status thymico-lymphaticus, five of simple goitre, fifteen of myxœdema (two of his own, and thirteen in the literature), thirteen of disease of the hypophysis (three of his own, ten in the literature), and five of Addison's disease (two of his own, three in the literature).

Borchardt found that in all diseases of the glands of internal secretion there was in the great majority of the cases an increase in the mononuclear cells, especially of the lymphocytes. There was leucopenia in about half of the cases, and approximately as often eosinophilia.

Since in all diseases of the thyroid, hypophysis and adrenals signs of status thymico-lymphaticus were established he concludes that the changes in the blood-picture are to be assigned to a status lymphaticus.

My observations do not permit me to accept in toto the views of Klose, Borchardt and the many others who attribute the lymphocytosis to the thymus. Of the 47 or more cases above referred to, operated upon during the past 20 years, in which I found it necessary to remove both lobes of the thyroid gland in order to relieve sufficiently the symptoms, about one-half have returned within the past two years for examination. In all of these, with perhaps two or three exceptions, the blood-picture is approximately normal. Of particular interest are the findings in a case at present in the hospital operated upon two years ago (double thyroid lobectomy). This patient was so ill when first admitted to the hospital, that I debated for some days as to the advisability of performing a lobectomy without the preliminary ligation of arteries. Her symptoms were predominantly vago-tonic but there were no signs of enlargement of the thymus. There was a mononucleosis of 53 per cent.

* These and many other cases controvert the opinion of von Lier who regards a lymphocytosis of 40 per cent as a contraindication to operation.

† Borchardt, Über das Blutbild bei Erkrankungen der Drüsen mit Innerer Secretion und seine Beziehungen zum Status thymico-lymphaticus. Deutsches Archiv f. klin. Med., Bd. 106, 1912.

The improvement which followed the resection of one lobe being unsatisfactory the remaining lobe was excised. The blood-picture was at the time only slightly altered by these operations although there was marked improvement in her general condition.

Now, after two years, she was returned to the hospital for examination. She is almost restored to health and is able to perform all of her laborious household duties. She complains particularly of a sense of pressure behind the manubrium to which she attributes in a measure her shortness of breath at times. Percussion and the X-ray now indicate definitely an enlarged thymus. The blood-picture is, however, normal (mononucleosis 30 per cent).

Another patient (Miss. G. C.) has just come on for re-examination from Texas, in response to a telegram from me. A year ago when admitted to Dr. Barker's service in the hospital she was acutely and desperately ill and was promptly transferred to the surgical side. The thyroid arteries were ligated, two at a time, and then, one after the other, the thyroid lobes were resected. Vago-tonic and sympathico-tonic symptoms were about equally pronounced. There was extreme exophthalmus with all the eye-signs. Pulse 140-150; slight enlargement of the heart. Sweating, diarrhoea, nausea and vomiting, intestinal gas, bad dreams. Dyspnoea, vertigo and very severe muscular cramps. Mononucleosis 51 per cent. There was no evidence of thymus enlargement.

Now, after a year, she has gained greatly in weight, is, in fact, a little too fleshy. Her general health is fairly good and is gradually improving. But her condition is not satisfactory. Her pulse is 100-110, she suffers from dyspnoea on slight exertion, has very little energy and is greatly concerned about the exophthalmus which is still a conspicuous disfigurement.* The blood-picture is, however, normal (mononuclears 28 per cent).

From the facts gleaned at the autopsy table, from experiments on animals and above all from the results following primary thymectomies we have convincing evidence that the thymus gland may play an important part in Graves' disease, and in some cases assume the title role. Some of the most puzzling features of the disease are made possible of interpretation by the discovery of the influence which the thymus may exert.

That the secretions of the two organs concerned in the production of the Basedow picture have a relationship there can be little doubt. The injections and implantations in animals made by Svehle, Bircher, Bayer, Basch and Gebele demonstrate conclusively that the thymus and thyroid possess in common certain fundamental physiological properties.

Antagonistic factors are also at work in the two glands, the presence of which is indicated sometimes directly and sometimes indirectly by the behavior of other organs. There are

* May 26. Within the past two months the patient's thymus has been treated with radium and the X-ray. The improvement has been quite marvelous. The exophthalmus has almost entirely disappeared and the patient considers herself almost well.

few in this audience * who are not familiar with the already famous experiments of Gudernatsch. To tadpoles equally developed, he fed to some the thymus of the calf, to others the thyroid of beeves. As a result of the thymus feeding the tadpoles increased greatly in size without differentiation or change in form. The creatures fed with thyroid promptly put forth arms and legs and otherwise rapidly took on the features of the frog. In the relation of the thymus and thyroid to the genital sphere and to the adrenals we find indications of a possible antagonism of some sort between the two glands. It is a well-attested fact that gravidity exercises a favorable influence upon the symptoms of Graves' disease. Basedow, himself, made this observation. This would seem to indicate that in pregnancy, in which unusual demands are made upon the thyroid, an excessive secretion from this gland can be utilized.

Between the thymus and ovaries there is experimental evidence of a possible functional antagonism. Thus Paton, Soli, Klose, Vogt and others have observed after thymectomy an increase in the weight of the ovaries, and according to Tandler and Gross there is abnormal persistence of the thymus in eunuchs.

Eppinger † relates of a case of Graves' disease of mild form in which immediately after castration toxic symptoms of threatening severity set in. He states that in the literature (reference not given) he has found a similar case. Of like significance probably is the fact that during the climacterium a mild may be converted into a severe form of Graves' disease.

Four or five years ago I was consulted in the North Carolina mountains by a native woman (Mrs. B.) who stated that for the previous six months she had been able to swallow nothing but liquids and for a week or more nothing but water. She was greatly emaciated and so weak that she could hardly stand. She was confident that the obstruction was just behind the "Adam's apple." The thyroid and cricoid cartilages were strikingly prominent, so much so that I confidently expected to feel a carcinomatous mass back of the larynx. I could feel nothing, however, except possibly an indefinite, soft mass of the presence of which I was not absolutely certain. She refused to come to the hospital, saying that she preferred to die at home. A year later I was surprised to find her robust and in perfect health. The difficulty in swallowing began to diminish soon after her visit to me, and in a month or two she was able to take food of all kinds as well as ever. The relief seemed to come quite promptly after the complete cessation of the menses. I concluded that a retrotracheal or retroesophageal portion of thyroid had become enlarged during the climacterium.

As further evidence of an antagonism between the secretions of the ovaries and thymus we may mention the excessive lymphocytosis which has been observed by Klose to follow the injection of Basedow-thymus after oöphorectomy. Klose injected 5 cm. of thymus juice expressed from the gland of a

Basedow patient into a spayed bitch whose lymphocytes after castration had risen to 32 per cent. Immediately after the injection there developed symptoms of severe Basedow intoxication. Shortly before death, which occurred one hour after the injection, the lymphocyte percentage was 64.

In one of my dogs (No. 9) which for 16 months had been deprived of both thyroid lobes and all the parathyroids except a graft, Dr. McCallum found complete absence of spermatogenesis. The testis as a whole was atrophic and spongy, but the interstitial cells of Leydig, although inconspicuous and perhaps somewhat degenerated, were still present in abundance.

What, then, is the relation of the thymus to the thyroid in Graves' disease? As stated by Capelle, the thymus can hardly be an "Erfolgsorgan" (a terminal apparatus), which enlarges simply in response to a stimulus from the specific gland. It is not merely antagonistic or compensatory (loose terms) to the thyroid, for if so its excision should be attended with an increase of the Basedow-symptoms. These organs, have, however, some sort of reciprocal relation. The effect of excision of the thyroid upon the thymus and of the latter upon the former organ has not been definitely determined.

In the dog (No. 9) just referred to, in which both of the thyroid lobes and all of the parathyroids had been excised, the thymus was carefully examined by Dr. McCallum, who at that time could have had no knowledge of its possible importance in Graves' disease. His report is as follows:

There is quite abundant thymus tissue. In the thymus there are some cysts, one of them quite large and lined by ciliated epithelium. Ciliated cavities of small size are found quite frequently through the tissue. I do not see any Hassall's bodies unless these might represent them. The thymus is not in the acme of its development, but has undergone a certain amount of atrophy.

Tatum found that the thymus of rabbits atrophied after excision of the thyroid.

As to the effect upon the thyroid of total excision of the thymus there is also uncertainty. The histological picture presented by the thyroid, seven months after total excision by Dr. McClure of my staff, and Dr. Park, Dr. Howland's assistant, of the thymus in a puppy, æt. 3 months, seems to be identical with that obtained by Matti and Klose, and interpreted by them as hyperplasia. On comparing the sections of the thyroids of Dr. McClure's dogs, of the control with that of the thymectomized animal, I should say that the changes in the latter indicate overactivity. These changes consist chiefly in entire disappearance of the colloid, and great increase in the height of the cells. The follicles are perhaps a little smaller in the hyperactive gland than in the control, and involutions are not conspicuous.

One can hardly be too cautious in assigning causes for the appearances found in one gland after excision of another, or in the remains of a gland after the resection of a part of the same. I am prompted to say this from experiences of my own, having particularly in mind our efforts to find the cause of the almost invariable hypertrophy of the thyroid in our dogs ex-

* This was delivered as a Harvey Lecture in New York early in 1914.

† Eppinger. Die Basedowsche Krankheit. Handbuch d. Neurologie, Bd. IV, Specielle Neurologie, III, p. 62.

perimented upon 26 years ago and to explain its absence after identically the same experiments during the past two years.

The pigmentation which has so emphatically arrested our attention in certain cases of Graves' disease deserves, I think, greater consideration than it has hitherto been accorded.

Our interest in this symptom has vastly increased now that we believe, I may say know, that the thymus may be an important factor in the disease.

As to the frequency of the occurrence of abnormal discoloration of the skin the statements of the various authors do not agree. Sattler, who gives the matter full consideration in his classical work on the symptomatology of Graves' disease, places it at 18 per cent. Kocher finds abnormal pigmentation of the skin once in 8 cases; Friedrich Müller observed it in 4 out of 5 of the serious cases. Murray noticed a more or less pronounced pigmentation of the skin 42 times in a series of 180 cases. There are some who think that this symptom rarely occurs. I have observed it chiefly in the instances of severe and of long-standing disease, and on reviewing the histories of my patients am impressed with the fact, as it seems to me, that the pigmentation has been more frequent in the vagotonic type of the disease.

This observation accords with what might be expected from animal experimentation and from the relation which has been observed by pathologists and clinicians of the thymus to the adrenals in status thymico-lymphaticus and in Addison's disease. Dr. Samuel J. Crowe of my staff, finds as a result of careful search of the records of the pathological department of the Johns Hopkins Hospital that in all the cases of status thymico-lymphaticus there is a note to the effect that the adrenals were atrophied, and that in Addison's disease hypertrophy of the thymus is almost invariably recorded.

Boignet and Calogero and Matzoukis found that excision of the adrenals was followed by hypertrophy of the thymus. Soli, Matti and, I think, Klose noted enlargement of the adrenals after thymectomy. Wastenson states that involution of the thymus may occur in consequence of the injection of the extract of the medulla and cortex of the adrenals. Possibly the extract of the medulla alone might have produced similar results, for Matti states that it is the medullary portion of the adrenals which hypertrophies in dogs deprived of the thymus gland.

Matti found, further, in his own laboratory an indirect confirmation of the above mentioned experimental data in that two animals with strikingly pronounced thymus-hyperplasia following extirpation of the spleen showed an extraordinary diminution in the amount of adrenal-medulla. In this constant reaction between the thymus and adrenal glands depressor influences are espied.

Treatment. Primary thymectomies uncomplicated by strumectomy, and secondary thymectomies in cases not sufficiently relieved by resection of both lobes of the thyroid would be the operations of choice for those searching for the essence of the Basedow thymus. The combined operation would be avoided by them as much as possible until it became more definitely known how profoundly and in what particulars the thymus may influence the disease. The excision of even a very small

piece of either gland for microscopical examination, in the course of operation upon the other, might vitiate the experiment. For example, in our case 2 (boy æt. 13) the resection of a portion of thymus hardly larger than one's thumb was followed by almost complete relief of the symptoms, including a return of the blood-picture to normal—symptoms which would be considered thymo- rather than thyrotoxic.

We are debating what should be done in a case desperately ill in which there are reasons for believing that the thymus is enlarged. Should we first ligate the thyroid arteries at one or more operations or perform primarily a thymectomy? * The ligation of one and perhaps even of two arteries is less of a proceeding than the excision or resection of the thymus, but is it not possible that the removal of a part of the gland the more specifically responsible for the disease might be better withstood by the patient than an operation of less magnitude upon the other? In our Case I, for example, the ligations of the inferior thyroid arteries were followed by very little reaction and by great improvement in the general condition of the patient. Would it not have been better, we are asking ourselves, to have performed a thymectomy with her primarily in this case, or in preference to the thyroid lobectomy which was done subsequent to the ligations? The patient, you will recall, died suddenly one day after the strumectomy. These are questions to which further experience must give the answer.

I may say that except in the instance reported (Case I) we have had no death from a lobectomy which had been preceded by preliminary ligation of one or more of the thyroid arteries. And even in the case just cited I am inclined to think that death might not have occurred had I ligated the superior as well as the inferior vessels. I believe from my own experience that, disregarding for the moment the question of thymus resection, we have absolute proof of the advisability of ligating the thyroid arteries, as advised by Kocher, in the severest forms of Graves' disease, indeed in all cases where there seems to be the slightest ground for fear that the patient might not withstand the lobectomy. Most surgeons have abandoned or not practiced preliminary ligation of the arteries, contending that the repeated operations are more troublesome to the surgeon, are unpopular with the patient and yield no better results. As to the last point I am sure they are mistaken; as to the weight to be attached to the other two, each must be his own judge.

From the point of view of the research worker the combined operation, thyroidectomy plus thymectomy, should, as I have said, not be done, but when having excised one lobe of the thyroid I have found myself actually confronted at the operating table with an enlarged thymus I have felt compelled for the patient's sake to resect it.

There is much reason for hope that radium and the Roentgen-ray may give us the solution of this question. The blood of Basedow patients who have been treated with the X-ray

* May 26, 1914. For the past two months we have been treating the thymus gland of selected cases of Graves' disease with the X-ray. The results will be reported later.

shows remarkably little mononucleosis (Klose). Klose, Arella, Heinke, Peters and others have shown that under the influence of the X-ray the thymus rapidly undergoes involution, an involution which is so extensive that Klose expressly warns against radiation of the thymus region in children. The relative absence of lymphocytosis in Basedow patients whose goitres have been treated with the X-ray is attributed by Klose to the influence of the rays upon the thymus. In a case referred to earlier in the lecture it was mentioned that two nodules, remains of the thyroid isthmus vanished promptly after prolonged exposure of the thymus to 1300 mg. of radium. The gradual enlargement of these nodules had caused the patient great anxiety, and she was the first to notice that they had disappeared. Furthermore, she no longer experienced the

feeling of oppression behind the sternum which had been a source of constant annoyance and occasionally of distress.

I have touched my subject only very lightly at some of the higher points. Hardly enough has been said even to make it clear that an enormous amount of work underlies the facts which we at present possess. It must be evident to everyone, however, that there reigns the greatest confusion on the subject of the function of the glands of internal secretion.

Fortunately the ardor for research on our globe is not diminished by the conviction that we are laboring in the wake of workers infinite in numbers on countless worlds who have carried their investigations millions of years beyond the stage reached by us, and are rapidly progressing towards an ultimate solution which may never be reached.

A SUMMARY OF STUDIES OF LOCO-WEED DISEASE OF SHEEP.¹

By HARRY T. MARSHALL, A. B., M. D., Charlottesville, Va.

Eleven years ago, during the summer of 1903, I was engaged by the United States Department of Agriculture to investigate loco-weed disease in Montana, and I continued this study during the summer of 1904. The data thus obtained were worked up into two reports to the Department of Agriculture submitted in 1904 and in the spring of 1906. A more complete technical report was also submitted to the Department. The reports have not been published by the Department, and recently Secretary Houston has given me permission to publish elsewhere. The full details of my studies will soon be published in the Bulletin of the Philosophical Society of the University of Virginia, Vol. I. In this article I shall give a brief review of my detailed report.

Widely spread over the western ranges from Canada to Mexico and from Kansas to California are many plants called loco-weeds. The plants properly called loco-weeds conform to two or three main types, all of which are members of the family Leguminosæ. These plants are hardy; bloom luxuriantly in the early summer and maintain themselves even where the soil is very poor, being most abundant, probably, in the higher plains and foothills east of the Rockies though not limited to this locality.

According to popular opinion, animals which feed upon these plants are attacked in the most remarkable way. They become crazy, hence the name "loco" or "crazy" disease; they are affected by the most peculiar mental and nervous symptoms; they become drug fiends, in that they want little else than the loco-weed to eat; they sooner or later emaciate and die from exhaustion or intercurrent disease. The length of the disease is not clearly described and many of the symptoms are extremely vague. Animals are supposed to teach one another the habit of eating loco-weed and often the disease will go through an entire herd or flock. The disease entered the United States from Mexico in the early stock-raising days of the west and gradually swept north and now it is found as

far north as Montana. The losses resulting from it are supposed to be perfectly enormous, partly directly by death, but to a greater extent from the depreciation of the animals which are supposed rarely to recover.

Experimental studies upon the loco-weed and feeding experiments have given the most contradictory results, but it is safe to say that no one has succeeded in definitely identifying any poisonous principle, inherent in the loco-weed, and capable of producing the symptoms popularly associated with loco disease.

My studies were confined to the locoed sheep of Montana. Other locoed animals could not be obtained for study even after extended search for them. Most exhaustive inquiries were made of stock raisers concerning various aspects of the symptoms, the etiology and course of the disease. These inquiries alone served to show that stock raisers had not a single clear cut disease in mind in describing loco disease; the description of one stockman not tallying with that of another. It appeared probable from studying as a composite picture the information thus obtained that loco disease was something in the nature of an infectious process or at least that it was communicable, and that it attacked especially the younger and weaker animals and prevailed more particularly over ranges and feedings grounds which had been in use for ten or more years.

An important part of my work consisted in inspecting flocks of sheep suffering from loco disease and in examining in detail the most typical cases of severe loco selected from these flocks. Detailed autopsies were performed upon the selected animals after the symptoms had been studied as carefully as possible. The autopsy tissues were studied microscopically. It was hoped that these studies would establish positively the symptoms of loco-weed poisoning, and would reveal any anatomic changes resulting in animals which were victims of the locoweed.

It soon became evident that the "locoed" sheep from different flocks were not affected by the same disease. One flock, for example, presented emaciation and weakness as the chief

¹ Published by permission of the Secretary of Agriculture.

symptoms, and at autopsy these sheep were found to be heavily infected with a tapeworm of the liver, "*Thysanosoma actinioides*."² A second group of sheep which were supposed to be typical locoes were overcome with bronchitis and respiratory distress. In these cases lung worms and pneumonias were very common. A third group of sheep whose behavior was regarded as most typical of locoed animals were found to be suffering from nasal and respiratory difficulties which were definitely proved to be associated with severe sheep fly infection (*Oestrus ovis*). A few other forms of parasite were encountered but the above mentioned were the most significant. In addition to these infections it became clear from inspection and from careful inquiry of the stock raisers themselves that the sheep in Montana, generally speaking, were insufficiently nourished. The ranges are grazed over so frequently that the grass does not have a chance to attain a good growth in the intervals between grazings; the flocks are too large for the available grazing grounds, while the grazing grounds are becoming curtailed as more and more open range is fenced in. Moreover in a large flock the delicate sheep have little chance to obtain good nourishment as they are crowded into the background by the stronger sheep.

A most careful study of the sheep failed to reveal anything in the least distinctive of the hypothetical loco poisoning either clinically or anatomically. The locoed sheep presented not a uniform picture as of a single disease, but varied appearances as from different diseases, any of which may be called loco disease by the ranchmen. The abnormalities observed in the selected specimens which I studied could be completely and satisfactorily accounted for by the evidence presented of underfeeding and parasitic infection. Moreover, a few very ill sheep, which were regarded by the ranchmen as typical examples of severe loco-weed disease, were kept under observation, and exhibited a distinct distaste for the loco-weed. At autopsy they were found to be emaciated, and to be infested with parasites. I therefore concluded that the animals which I had observed, although called locoed sheep by expert western ranchers, did not owe their condition to loco-weed poisoning, but were, in fact, examples of poorly nourished sheep, usually suffering from parasitic infection.

During 1904, in addition to continuing the examination of locoed sheep, an experiment was carried out of rather an elaborate nature in an attempt to produce pure loco disease in sheep by feeding them upon loco-weed. A tract of public land upon which the loco-weed, *Aragallus spicatus* (Hook.) Rydberg, was very abundant, and where no other poisonous plant could be found, was fenced in and divided into several lots. Eighty sheep—lambs, ewes and yearlings—were selected from a healthy looking flock and were dosed thoroughly with thymol and creosote in order to rid them of parasites. They were then divided into several groups and placed in a series of corrals.

²The diseases produced in sheep by *Thysanosoma actinioides* formed the subject of a paper presented by me before the Association of American Pathologists and Bacteriologists in April, 1912, in which I described a new form of biliary hepatitis due to infection with this tapeworm.

The sheep in some corrals were not allowed to eat loco-weed, but were fed abundantly with alfalfa hay. A second group were given only one-half rations of alfalfa hay, but no loco-weed. A third group were given no alfalfa hay, but plenty of loco-weed. A fourth group were given one-half rations of alfalfa hay and plenty of loco-weed. Another group were given plentiful rations of alfalfa hay and were also allowed to feed freely on loco-weed. The experiment was continued from July 15 to September 6, 1904, 54 days. The details of this experiment are recorded elsewhere. It will suffice to summarize the results here.

It appeared that the healthy sheep did not eat the loco-weed if they could easily obtain a plentiful supply of green forage, but it was easy to force them to adopt a loco-weed diet by reducing their food, or by reducing available green forage, even when the animal was given a plentiful supply of cut alfalfa hay. When once the animal had started to eat the loco-weed, in no instance did it appear to eat it to the exclusion of other food, although the animals may eat rather more of loco-weed than of any other single plant and may show rather a preference for it. In no instance did an animal eating the loco-weed exhibit any characteristic symptoms.

The animals which were not given alfalfa but were forced to feed on the loco-weed and the small amount of other forage in the corral suffered markedly from starvation. It was clear that this was no specific effect of the loco-weed because the animals receiving abundant alfalfa and also eating abundantly of loco-weed kept in much better condition and gained more in weight than those animals receiving only alfalfa and not eating loco-weed. In other words it appeared from this experiment that alfalfa and loco-weed is a better food for sheep than alfalfa alone and moreover it appeared that loco-weed alone does not keep the animal in a good state of nutrition.

Several other interesting points were indicated by this experiment. The sheep were divided into sets, some of which received salt regularly and others did not receive any salt during the course of the experiment. Strangely enough the animals which received salt gained less in weight than those which were unsalted, and among the animals which lost weight the unsalted lost less weight than the salted animals. The young animals were more severely affected by the insufficient diet than the adult sheep.

During the course of the experiment sheep fly disease (Myiosis), attacked all the corrals and was exceedingly severe in its effects upon the starved animals while the better nourished ones escaped with little damage, the sheep receiving alfalfa and loco-weed suffering less than any others.

The outcome of this experiment was to convince me that none of the abnormalities encountered in the sheep which I had studied could be attributed to the poisonous action of the loco-weed. None of my sheep gave the slightest evidence of having suffered any ill results from eating the weed. On the other hand the experiment seemed to confirm the view advanced in 1903 that the animals were suffering chiefly from starvation combined with one type or more of parasitic infection.

My conclusions are at variance with the opinion held by members of the United States Department of Agriculture and further experiments have subsequently been conducted on the most elaborate scale by Crawford and Marsh. Crawford's work which led to the conclusion that the symptoms of loco disease are due to barium poisoning was soon upset by a publication by Alsberg and Black from the Department of Agriculture. Marsh's work is hitherto the last word from the Department on the subject of loco disease. I have gone most carefully and painstakingly over the available reports from Marsh and his colleagues and find that the several reports contain perplexing contradictions, and are lacking in important scientific details which it is necessary for Marsh to supply before his conclusions can be accepted. So far as I can make out from a careful study, Marsh claims that he has been able to produce with regularity, definite and fatal forms of poisoning in sheep, horses, and cattle by feeding them for a long time on loco-weed. Very few of his animals developed symptoms of locoism until they had been feeding on loco-weed longer than had my experimental sheep. He claims that there are definite and diagnostic symptoms which can be easily recognized when once they have been seen, and moreover—which is even more important, he claims that there are diagnostic anatomic changes in the animals which have died of loco poisoning. These anatomic changes consist essentially in ulceration and congestion of the stomach of horses or of the fourth stomach of sheep and cattle; of pronounced anemia; and of what are spoken of as serous collections around the heart and around the spinal canal outside of the dura mater. In the latter situation the so-called serous collections are frequently found in a state of organization. In addition there are frequently hemorrhages into the ventricles of the brain. In my more elaborate report I have analyzed carefully the writings of Marsh and have come to the conclusion that Marsh has by no means established the fact that the conditions he describes are due to loco-weed, and that up to the present time his work must be taken as a further substantiation of my claim that "loco disease" is not a clinical entity, because he has added one more to the list of diseases which go by the name of "loco-weed disease." Until Marsh gives definite and con-

clusive reports upon the nature of these remarkable spinal coagula and definitely excludes the possibilities of spinal meningitis and meningo-encephalitis, and until he fulfils other necessary requirements it cannot fairly be claimed that he has established loco-weed disease either as a clinical or as a pathologic entity.

The situation as it now stands is about this: The western ranchmen have for years been suffering heavy losses which have been attributed to the poisonous action of the loco-weed.

The Department of Agriculture, through Marsh's publications, has adopted the view that the ranchmen are correct in imputing their heavy losses to the loco-weed. Marsh urges the launching of a very expensive campaign against the loco-weed, with the object of eradicating it, a campaign for which I can find no reasonable justification.

My investigations have convinced me that there are several diseases of western livestock masquerading under the general name "loco disease." One hundred per cent of the severely "locoed" sheep which I studied were not suffering from locoism, but from underfeeding combined with parasitic infection. I therefore think there is reason to be doubtful as to the existence of pure, bona fide loco-weed poisoning, and I hold that it is perfectly certain that the heavy losses attributed to loco-weed disease, are at least in large measure due to other causes, which can usually be ascertained by careful study.

My investigations have brought to light several dangerous parasitic diseases of western live stock, and I have emphasized the fact that it is common for the animals to be distinctly underfed. My conclusions have received support during the last ten years through several publications from the Bureau of Animal Industry, dealing with various parasitic diseases of western live stock. A study of the literature upon the subject, and of the works of Marsh and Crawford, and a review of my own work leads me to believe that the very serious losses which occur among western live stock raisers demand attention, and that their interests can best be served, not by a blind assault upon the loco-weed, but by a vigorous campaign directed first at combatting the overstocking of ranches and the underfeeding of stock, and second at combatting the parasitic diseases prevalent over the western ranges.

NEW PUBLICATIONS.

The following six monographs:

Free Thrombi and Ball-Thrombi in the Heart. By J. H. HEWITT, M. D. 82 pages. Price, \$1.00.

Benzol as a Leucotoxin. By LAURENCE SELLING, M. D. 60 pages. Price, \$1.00.

Primary Carcinoma of the Liver. By M. C. WINTERITZ, M. D. 42 pages. Price, 75 cents.

The Statistical Experience Data of the Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By FREDERICK L. HOFFMAN, LL.D., F.S.S. 161 pages. Price, \$2.00.

The Origin and Development of the Lymphatic System. By FLORENCE R. SABIN. 94 pages. Price, \$2.00.

The Nuclei Tuberis Laterales and the So-called Ganglion Opticum Basale. By EDWARD F. MALONE, M. D. In press.

are now on sale by THE JOHNS HOPKINS PRESS, Baltimore. Other monographs will appear from time to time.

THE BEHAVIOR OF AMŒBIC DYSENTERY IN LOWER ANIMALS AND ITS BEARING UPON THE INTERPRETATION OF THE CLINICAL SYMPTOMS OF THE DISEASE IN MAN.

By WALTER ALBERT BAETJER, M. D.,

AND

ANDREW WATSON SELLARDS, M. D.

(From the Medical Clinic of The Johns Hopkins Hospital.)

OUTLINE.

- I. Introduction.
- II. Synopsis of the literature:
 1. Spontaneous occurrence of amœbæ in lower animals.
 2. Reproduction of certain clinical features of amœbiasis in lower animals:
 - a. Acute infections.
 - b. Liver abscess.
 3. Failure to reproduce chronic infections with relapses or the carrier state in lower animals.
 4. Appearance of symptoms, especially septicæmia, which are not described in man.
- III. Behavior of typical strains of amœbæ in animals:
 1. Material for study. Inoculation of six strains in forty-seven animals.
 2. Reproduction of certain features occurring in human cases:
 - a. Acute fatal infections.
 - b. Chronic infections with relapses.
 - c. Carrier state.
 - d. Liver abscess.
 3. Features in human cases which have not been produced in animals:
 - a. Intestinal amœbiasis with extensive lesions, but without dysentery.
 - b. Rarer complications of dysentery, such as brain and splenic abscess.
 4. Features common in animals which have not been described in man: septicæmia:
 - a. Relation of septicæmia to therapy.
 - b. Relation of septicæmia to cause of death in amœbic infections.
- IV. Behavior of atypical strains in animals:
 1. Atypical features observed in man:
 - a. Continuous course of symptoms without intermission.
 - b. Absence of blood from stools.
 - c. Unusual morphology of the amœbæ.
 2. Infection of ten animals with three atypical strains with reproduction of atypical features.
- V. Comparison of gross pathology in man and animals:
 1. Difference in distribution of the lesions.
 2. Characteristic features of the acute and the chronic lesions.
 3. Behavior of atypical strains.

INTRODUCTION.*

In the relationship between the infectious diseases of man and the lower animals many gradations, in regard to transmissibility, occur between the extremes of absolute immunity and pronounced susceptibility. In one group we find those diseases of man which the lower animals contract spontaneously with the reproduction of the typical clinical picture.

* For all of the inoculations directly into the lumen of the bowel, a laparotomy was done under general anæsthesia (ether). B. & S.

At the other extreme we have those diseases of man to which all other species are not only naturally insusceptible, but to which they remain absolutely refractory, in spite of all predisposing factors that have been used to induce an infection. Conversely, it is even safe to assume that there are diseases which are absolutely specific for lower animals and which cannot be transmitted to man under any ordinary conditions. In this connection it has been found that experimental amœbic dysentery in lower animals runs a course which is strikingly similar, even in the finer details, to the rather complex course of the disease as it occurs spontaneously in man. Indeed, this similarity is so great that the study of the disease in lower animals is of direct value in the interpretation of the features that occur in man.

SYNOPSIS OF THE LITERATURE.

The spontaneous occurrence of amœbæ in lower animals is fairly common. The saprophytic amœbæ of the limax group occasionally pass mechanically through the intestinal tract when ingested with food. They are of no interest, however, except that they have occasionally been mistaken in cultures for the parasitic entamœbæ. They are not known to colonize in the intestinal tract in any animals, except possibly in certain marine fishes.¹

The predominant types of amœbæ found in the lower animals are members of the obligately parasitic, but non-pathogenic, genus of entamœbæ. These occur in widely different groups such as the mammalia and amphibia. Occasionally one finds spontaneous infections in dogs and monkeys with pathogenic entamœbæ with the production of typical clinical symptoms, though the disease apparently does not occur epidemically or endemically among the lower animals.

Amœbic dysentery has been produced, in isolated instances, in a variety of lower animals, more especially in cats, dogs, and monkeys, but for extensive work, cats have been used almost universally. Some of the most important features of human amœbiasis that have been obtained in cats are (1) acutely fatal infections, and (2) the spontaneous occurrence of liver abscesses in infected animals. Certain prominent features, however, have not been observed in infected animals. Typical chronic infections have not been produced. It is hardly possible that the susceptibility of cats is so great that chronic lesions do not have time to develop, for many individuals are comparatively refractory. The experience of Craig² and Wenyon³ may be taken as illustrating the usual behavior of infections in cats. In a comparatively large series of animals chronic infections did not develop. The longest

duration of the disease was four weeks and the remissions typical of the disease in man were not observed.

On the other hand, certain features have been observed in infected animals which have not been described in human cases though their occurrence in man is not improbable. Among the more important of these is the frequent occurrence of septicæmia in acute infections.

Clinical Course in Animals.—Observations were made upon the course of the disease in animals both upon the first transfer of various strains from patients to kittens, and also after the passage of a strain through a series of animals. This gave an opportunity to study the action of strains of varying degrees of virulence; and of strains the specificity of which for kittens had been modified to a variable degree by passage through a series of kittens. The following outline gives a summary of the material on which the observations in this paper are based:

ANIMAL INOCULATIONS.

Source of Strain	No. Inoculated	No. Infected	No. of Failures	No. Dying in Incubation Period	No. of Passage in Animals
North Carolina...	6	2	..	4	1
Panama City.....	3	2	1	..	1
Panama City.....	1	1
West Indies.....	6	3	3	..	3
Philippines.....	36*	27	4	5	11
North Carolina...	2	1	1
North Carolina...	3	2	1
North Carolina...	3	1	..	2	..
North Carolina...	1	1

* Four animals of this group were guinea-pigs. All the remaining animals in this table were cats or kittens.

In all, nine strains were inoculated successfully into animals. Of sixty-one animals inoculated, forty contracted an infection. Six of these strains were typical strains obtained from patients with symptoms of varying intensity. They were inoculated into cats and subinoculations were obtained with two of these strains. These patients had contracted their infections in widely separated regions: one came from the West Indies, one from the Philippines, two were from Panama City, and the remainder from the Southern States. All of these strains were transmitted successfully to cats. Forty-seven animals were inoculated, of which thirty-two developed definite clinical symptoms accompanied by the presence of active amœbæ in the intestinal discharges. The initial attack was sometimes preceded by a prodromal day of diarrhœa, though frequently at the onset formed stools were accompanied by bloody mucous discharges, the gross faecal matter often being replaced soon by blood and mucus. In kittens the disease was uniformly fatal, most often in the first attack. In adult animals the initial attack was seldom fatal, the course being usually subacute or chronic and often ending in recovery. The animals which died acutely were of interest on account of the almost constant development of septicæmia and its bearing on the cause of death. The chronic cases were of interest from several standpoints. Some corresponded closely to chronic human cases, periods of apparent health alternating with acute relapses. In the interim

between the attacks, the animals were free from symptoms, the stools were normal in gross appearance, and were frequently negative on microscopical examination; in such instances it was not possible to make a diagnosis of amœbic infection between attacks. In two adult cats a carrier state developed, the amœbæ persisting in one animal for three weeks, and in the other for two months without symptoms of dysentery. These two terminated in complete recovery. This carrier state developed only after an acute attack of dysentery had occurred; *i. e.*, there was no case in which animals were parasitized without producing clinical symptoms, though no specific attempts were made to obtain such a result. In a large number of human infections, Walker⁶ found that individuals frequently became parasitized with *E. histolytica* and remained carriers over long periods, but without the development of symptoms. Clinically, such cases corresponded exactly in their behavior to cases of infection with *E. coli*.⁶

A few conditions have been described in man which have not been reproduced in animals. One of great importance, if substantiated, is the occurrence of intestinal amœbiasis, with the production of intestinal lesions, often sufficient to cause death, but without any symptoms of dysentery. Although such cases have been described in the literature, we feel that it would be extremely difficult to establish the authenticity of such a condition on evidence which is wholly free from objection. No evidence has been obtained in any of this experimental work in support of such a condition. In the infection in cats, dysentery was an early and prominent symptom. We obtained amœbic infections in guinea-pigs in which a secondary bacterial peritonitis developed without any symptoms of dysentery. This, however, is not comparable to the course of the fatal cases in man with extensive amœbic lesions, as described by Musgrave.⁷

The other conditions found in man which have not been reproduced in animals may be classified under the head of the rarer complications of dysentery depending upon secondary bacterial invasion. Examples of this are seen in the development of a brain abscess and of a splenic abscess. These conditions occur but rarely in man and their reproduction in animals would be of interest only from the standpoint of a curiosity. Indeed, in two guinea-pigs which we inoculated with *E. histolytica*, a peritonitis developed which proved fatal three days after inoculation. Examination of the stools of the animals at the time of inoculation showed no amœbæ. At the autopsy, *E. histolytica* was found at the site of the lesion in the bowel, which consisted in an area of inflammation without ulceration. The intestines were matted together around this lesion, and a bacterial peritonitis had developed which was becoming generalized. Two additional guinea-pigs were injected with a bloody mucous stool from a kitten. One of these remained well and the other died of a bacterial peritonitis ten days later. In addition to the localized inflammation of the bowel there was an area of definite ulceration and typical entamœbæ were found in the ulcer. However, there were no symptoms of dysentery, and no blood nor mucus appeared in the stools.

The infection of rodents is of interest in that they have not been used for the experimental study of amœbic dysentery and it is even reported that they are insusceptible to infection.⁸ The advantage of using rodents would be obvious. However, we feel from this limited experience that although they are not resistant to pathogenic amœbæ, yet they are unsuitable for experimental work, both on account of their marked susceptibility to secondary bacterial invasion and also because they do not present typical symptoms of dysentery.

Liver Abscess.—In one case, an extensive liver abscess developed, occupying about one-quarter of the entire liver. This was found at autopsy in an animal dying six and a half weeks after inoculation. The initial dysentery had never cleared up completely and many motile amœbæ were found in the intestine at the time of death. Motile amœbæ were extremely abundant in the lesion in the liver. Stained smears showed no bacteria, but upon inoculation into nutrient media, a small micrococcus grew out in the majority of the tubes. This lesion, strictly speaking, was not an abscess, but consisted in extensive necrosis of the liver with beginning caseation. The important feature from a clinical standpoint, was that no fluid was present. Such a lesion would, of course, give the classical signs of liver abscess, yet upon exploration no fluid would be obtainable by aspiration and it might be impossible to confirm the diagnosis unless one were fortunate in securing a little necrotic tissue in the aspirating needle. The occurrence of extensive necrosis without abscess formation offers a ready explanation for the discrepancy which sometimes occurs between the physical signs and the findings at operation.

The one prominent feature of the animal infections which apparently has not been described in man is the frequent occurrence of septicæmia in the acute cases. In the case of the most virulent strain, septicæmia occurred in practically 100 per cent of all the young animals inoculated. In regard to human infections there is sufficient evidence to warrant the conclusion that septicæmia must occur at least occasionally. The bacterial invasions of the liver may, of course, be the result of an occasional embolus. In cases where a gangrenous bowel or a peritonitis develops, the probability of a terminal septicæmia is very great. The rare cases of brain or splenic abscess suggest very strongly that a septicæmia of longer or shorter duration was present. Finally, Strong has found that cultures of the heart blood taken post mortem, in cases of dysentery show the occurrence of secondary invasion by bacteria.⁹ In connection with the significance of septicæmia, an instructive condition occurred in one animal. An acute, fatal attack of dysentery followed an injection by a high rectal tube. At autopsy, it was found that an extensive empyema had developed on the right side, and the pericardial sac was distended with yellow purulent fluid. Such a complication of a septicæmia suggests the existence of a general group of cases which give a history of typical amœbic dysentery accompanied by evidences of septic processes with suppuration in various parts of the body, as in the lung, the kidney, or other organs. The occurrence of septicæmia is of importance from two standpoints. In the first place, it was not possible to prove, experi-

mentally, that amœbic infection of the intestine was capable of causing death by the primary action of the amœbæ. Indeed, the evidence pointed toward the contrary. Where death occurred it could always be explained by other factors; with one exception, death was due to secondary bacterial invasion. When such secondary invasion did not occur, the animals eventually recovered. If septicæmia occurs at all frequently in the acute fatal cases in man, it would have a very direct bearing, both upon the cause of death of such cases, and upon the explanation of the inefficiency of emetine therapy, which Rogers¹⁰ has so frequently observed. The high leucocytosis (20,000 to 30,000) which is the rule in such cases is rather more suggestive of a bacterial than of a protozoan infection.

Behavior of the Atypical Strains of Dysentery.—Not only were the prominent features of dysentery reproduced for typical strains, but two distinctly atypical strains behaved in a remarkably similar atypical manner upon inoculation into animals. The following are the essential features of the most important case. A negro from the West Indies came to the hospital on account of a persistent diarrhoea which was sufficient to incapacitate him for work. He was passing eight to ten fluid stools per day, which were free from blood and practically free from mucus. The onset of the intestinal trouble occurred about ten years ago. In the early years of the disease, the stools were frequently bloody. In the past year the condition had been progressing slowly, there being no intermission in the symptoms, with periods of apparent health, such as are characteristic of amœbic infection. The general strength and health of the patient were good notwithstanding the intestinal trouble. Upon physical examination, a thickening of the sigmoid could be felt through the abdominal wall. Proctoscopic examination showed a thickening of the rectum, such as occurs in a syphilitic process. The Wassermann reaction was positive. Daily examination of the stool showed numerous flagellates, and after a saline purgation, one or two motile amœbæ were occasionally found. In specimens stained with hæmatoxylin, a few trophozoites were found after examining several slides. The nucleus of these was distinctly different from that of the usual pathogenic forms and the parasite could not be identified morphologically with any of the commoner types. Persistent attempts at cultivation, according to the usual technique, over a period of three weeks were uniformly negative. In addition to the 2 per cent of normal alkali which is usually added to the media, we employed varying percentages, from 0 to 2 per cent.¹¹ Conditions of cultivation were fully controlled. A culture of limax which had not been transplanted for more than two years, was found to be viable and grew well on all the media which were used in the attempt at cultivating these amœbæ from the human case. Upon inoculation of this culture of amœbæ into the rectum of two kittens, microscopic examination of the stools on subsequent days was uniformly negative. This strain of limax, however, was recovered by cultivation from the stool for a period of four days in both animals. In this respect the behavior of limax in kittens corresponds essentially to its behavior in man.

A still more crucial test was obtained, for we were able to cultivate a limax from the stool of a normal kitten which had not been previously inoculated with the organism. It was evident from these failures at cultivation that this strain of amœbæ, occurring in the diarrhoeal stools of the patient, was not any ordinary strain of limax. Accordingly, an inoculation of stool was made at three sites; namely, into the cæcum, into the ileum one foot above the ilio-cæcal valve, and into the stomach. Six cubic centimeters were used for each injection. Microscopic examination of the material used for inoculation showed only one trophozoite, after the examination of several cover-slip preparations. Cyst-like bodies were present containing two and often three nuclei.*

After an incubation period of one month a watery diarrhoea developed in this kitten, accompanied by fair numbers of amœbæ. This diarrhoea continued without intermission and without the presence of blood or any significant amount of mucus. The general health and nutrition of the animal not only remained good, but its growth continued rapidly without any interruption. The morphology of the amœbæ changed definitely, the nucleus becoming poorer in chromatin, but still remaining very much richer than in the case of *E. histolytica* or *E. coli*.†

After these symptoms had persisted for two months, the animal was sacrificed and two kittens were inoculated intracæcally. The incubation period in these two animals was shortened to five days and ten days, respectively; the injected material, however, was much richer in amœbæ than in the first transfer from the patient. In the second passage more mucus was present in the discharges and occasionally a few blood corpuscles were seen microscopically. Transfers were made from the animal with the longer incubation period to two kittens, one of which was inoculated by rectal tube and the other intracæcally. Only the second animal became infected, the incubation period being reduced to three days. No attempt was made to carry this strain further.

A second atypical strain was studied which corresponded very closely to the one just described. The patient, who had never been south of Maryland, had had a constant watery diarrhoea for eighteen months. Proctoscopic examination showed several ulcerated points in the rectum. A kitten about half-grown was inoculated intracæcally with the stool of this patient, and after an incubation period of one month, a watery diarrhoea developed, which persisted with practically no intermission for one and a half months. Numerous amœbæ were found in the discharges, especially after purging with magnesium sulphate. These were characterized by a chromatin-rich nucleus. After two months the symptoms had practically subsided. The animal was sacrificed; anatomically, the intestine was normal. No amœbæ were found in the mucosa.

In a third case, a boy of 14 years complained of a condition which anatomically was a giant colon. The stools had been

constantly fluid for a period of eight years and frequently large blood clots were present. Microscopically, many flagellates and occasional amœbæ were seen. Morphologically, the trophozoites which were seen corresponded essentially to *E. histolytica*, except that there was somewhat more chromatin in the nucleus than one ordinarily sees. Injection into a kitten produced an acute bloody mucous diarrhoea of a few days' duration, which terminated promptly in recovery. Fresh specimens of stools were not obtained for examination and the amœbæ, which were seen, had evidently undergone degeneration.

Of the remaining strains which were studied, it may be said that the severity of the disease in the patient was a surprisingly good index of the virulence of the strain of amœbæ for kittens. Thus, chronic cases of long standing, with mild symptoms, often produced an attack in animals which was of comparatively short duration and eventually ended in recovery. Unfortunately, however, any strict comparison of the virulence of various strains for cats would be vitiated by the widely different ages of the animals which it was necessary to use.

The results with the atypical strains may be summarized as follows:

1. The incubation period was much longer than in the case of typical strains.
2. The clinical symptoms corresponded to those seen in the patient, the striking feature in some being the absence of blood from the stools and the continuous course of the symptoms without intermission.
3. The morphology of the amœbæ was atypical both in the patients and in the animals.

Comparison of Gross Pathology in Both Man and Animals.

—The pathological lesions in the animals infected with typical strains of amœbæ corresponded in their essential features to the changes that take place in man. The acute and chronic stages were comparable to corresponding stages in human cases. The most prominent feature about the lesions in cats was their rather strict localization in the lower fourth of the large bowel. This was true regardless of the type of lesion which occurred. Even in the most acute cases the anatomical lesions were limited to the lower portion of the rectum, though in these cases where the faecal contents were replaced by blood and mucus, numerous amœbæ were found throughout the lumen of the large intestine. Craig^{1,c} also reports that he found that the amœbic lesions in cats were most prominent in the rectum. No definite explanation suggested itself for this localization other than a remarkable specificity of the amœbæ. The most tangible difference that could be noticed between this portion and the middle or upper parts of the large bowel was the difference in consistency of the faecal matter at the different levels, for it is only in the lowermost portions that formed faeces exist. The predominant location of the lesions in man is just the reverse of this distribution in cats. Rogers,^{1,c} in his experience of twelve years at Calcutta, found that the most frequent location was just below the ilio-cæcal valve. Only in a small percentage of cases were the lesions limited to the

* In a single instance, after the examination of several slides, a four nucleated cyst was found.

† A full description of the changes in morphology will be discussed in a separate communication.

rectum. However, in some instances, in which the lesions occurred higher in the bowel, there were scars of old lesions in the rectum and sigmoid.*

Description of Lesions.—The acute lesions which occurred for the most part in kittens, consisted in diffuse hyperæmia, congestion, and œdema of the mucosa and submucosa, giving rise to a granulomatous appearance. The serosa over such areas was usually bright from the injection of the vessels. Death took place before there was time for the development of any appreciable degree of ulceration.

In chronic cases multiple ulceration took place. In some instances healing occurred before the ulcers had advanced very far; in some of the fatal cases there was moderate undermining of the ulcers, but the extensive gangrene of the bowel, such as occurs in man, was not observed.

Pathological Lesions in Atypical Cases.—The pathological lesions in the atypical cases resembled the very mild lesions of the typical strains. Hyperæmia and congestion with swelling of the mucosa were well-marked features in some instances, though no ulceration was observed at any time. In the strain from the West Indies, the cat used for the first passage had practically healed at the time an anatomical examination was made and was essentially in the stage of a carrier. Of the two cats used in the second passage, the gross appearance of the large bowel in one was normal at autopsy; in the other it was slightly hyperæmic, and there were small areas of hæmorrhage. Of the two cats used for the third passage, the bowel in one was also normal, and the other showed changes only in the lower half of the rectum, the characteristic feature being a well-marked diffuse hyperæmia. The two animals used for the second and third atypical strains did not show any gross changes in the bowel.

Although the formation of ulcers with these atypical strains was not observed, nevertheless, we are not inclined to feel that it constitutes a point of absolute difference from the typical strains. It would seem probable that ulceration is only less common with the milder strains. In this short series of animals it might easily have failed to appear, for in the larger series with virulent strains it was observed in a perfectly typical form in only three instances.

SUMMARY.

1. The course of amœbic dysentery in cats corresponds very closely to the typical clinical picture which occurs in man. The acute and chronic forms of the disease, with the produc-

* It is well to bear in mind the anatomy of the large bowel in the cat. It extends almost as a straight tube from the ileocæcal valve to the anus, lying practically in the mid-line.

tion of liver abscess and the carrier state, have been reproduced. No experimental evidence in cats was obtained which would suggest the occurrence of fatal intestinal amœbiasis without symptoms of dysentery. Rare curiosities, such as brain and splenic abscess, have also not been reported in animals.

2. Cases of intestinal amœbiasis which are remarkably atypical occur in man. Upon reinoculation of these strains into lower animals, infection takes place with the reproduction of the atypical features.

3. Extensive amœbic infection of the liver occurred in one animal with the involvement of about one-quarter of the liver substance, with extensive necrosis and caseation, but without the formation of any fluid. Such a lesion, occurring in the depths of the liver, would give all the typical clinical signs of liver abscess, but could not be diagnosed at exploration by aspiration unless liver tissue, obtained in the aspirating needle, were examined.

4. The acute and chronic types of lesions corresponded in the essential features of their pathology to human conditions. The localization of the lesions, however, was rather different from that seen in man.

5. Three of four guinea-pigs inoculated with pathogenic entamœbæ, contracted amœbic infection, but these animals proved unsuitable for study on account of the atypical course of the disease, and their susceptibility to secondary bacterial infection.

6. Bacterial septicæmia was a prominent factor in causing death in the infected animals. There are several features which suggest that it may play a more or less prominent part in the course of the acute cases occurring spontaneously in man.

7. No crucial evidence was obtained experimentally that *E. histolytica* is capable of causing a fatal infection in man in the typical course of the disease without the aid of secondary bacterial invasion.

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JOHNS HOPKINS HOSPITAL BULLETIN.

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IN MEMORIAM.

RUPERT NORTON.

1867-1914.

I knew him from the time he was seven years old. Shady Hill was the paradise of the boys and girls of Cambridge. In front of the old house so dear to generations of Harvard students who have received the kindly hospitality of his distinguished father—in front of the old house the land fell with a gentle inclination toward “Norton’s Woods”; and this little slope, the nearest approach to a hill in the flatness of Cambridge, was known to us all as “Norton’s Hill”—or “Norton’s” for short. “Norton’s”—what memories of delight that name brings! For there, on the winter days, within a few steps of the front door, all the boys and girls of Old Cambridge used to coast. No memory of my youth is more vivid. The welcome snow-storm; the laborious watering of the snow that the coast might be smooth and hard and icy; the rivalries with sled and “double-runner”; the unwelcome thaw. But above all, the glories of coasting by night; the beauty of the crisp, cold moonlight on the snow; the torches; the big double-runners; the older boys and girls, to whom we looked up with such awe and admiration—and envy when we, poor youngsters, were whisked home at an early hour. It is long years ago as I write, but it is still very near in my happy dreams.

At the bottom of the hill began “Norton’s Woods,” of refreshing memory. I wonder how many acres they covered. Not so very many, I fancy; and to-day they are in great part gone. But the fine old trees, the cool and mysterious shades, the rustling of the birds, are as fresh and real to-day as they were forty years ago. And so is the old house, with its long and leafy avenue, and the kindly face of its master, and the charming family circle.

It is with these scenes and memories that I first associate Rupert Norton. His brother Eliot and I used to pore over our stamp collections in the spring and fall, and in the winter we shared a double-runner. In those days Rupert, barely three years younger than we, seemed a little boy. He was then, as always, quiet and modest and reserved. Brought up at home in an atmosphere of books and art and scholarship, he entered college in the sophomore year. His life at Harvard was uneventful, his acquaintances not especially numerous but well-chosen and devoted to him. At the end of his college course he had a severe illness, and it was not until a year after his graduation that he began the study of medicine in Germany. There again our paths crossed, for at this time I also was spending a year in the laboratories and hospitals of Berlin. Our work was different and we met only occasionally; but when I was taken ill with diphtheria, he was at my side in a minute and was kindness and consideration itself. Helpful, thoughtful, self-effacing, he paid me all those little attentions which throughout life he has so unostentatiously showered upon his friends, and for which they feel so deep a gratitude.

After a year in Germany he returned to the Harvard Medical School where he finished his course in 1892, taking his degree in 1893, as was customary then for those who accepted hospital positions. After some months’ service in the Children’s Hospital of Boston, he came to The Johns Hopkins Hospital as assistant resident physician in the spring of 1893. The staff was then small; undergraduate teaching had not yet begun. His associates were Hewetson, Smith, Ramsay, Billings, Oppenheimer, Carter, Blumer, Futeher, Atkinson. Careful, faithful, thorough in his work, rather diffident in manner, he was not quick in making acquaintances; but before he left the hospital he was dearly loved by all of his associates. For behind the shy, diffident, rather abrupt manner, were hidden most lovable and charming qualities of mind and heart: a keen perception; a nice sense of humor; a most companionable, lovable, loyal nature—kindly and generous, charitable to a fault, intolerant only of that which seemed to him soft, unmanly or indirect.

In April, 1895, he left the hospital and began the practice of medicine in Washington—practice which was not rapid in coming to him; for he was too shy, too retiring, too reserved. and his peculiar reticence and even dryness of manner were too often interpreted as coldness and lack of interest. But those patients who came to know him, and the colleagues who broke through the shell of shyness and reserve, found one of the warmest, most generous and kindly hearts that ever beat. No one who knew Norton failed to love him.

In the Spanish War he enlisted as an Acting Assistant Surgeon and served throughout the campaign, doing, in the main, pathological work in one of the large Southern camps.

After this, to the disappointment of many of his friends, he gave up his Washington practice to become medical director of the Parisian office of a large American life insurance company. In his new work he displayed the same care and thoroughness that had been characteristic of all his endeavours. While many of us felt that the routine of this position was hardly worthy of one of his talent, yet in a way the situation had its advantages. The broad literary and artistic opportunities of Paris appealed to him deeply, and his life was far from empty. Outside of his work and other interests, Norton sought for and found opportunities to encourage and help his deserving fellow-countrymen of the artistic colony. How wise and thoughtful and discriminating his generosity was, few will ever realize, for his charity was known only to himself.

In 1906, the company with which he was associated abandoned its offices in Paris and Norton returned to the United States as Acting Superintendent of The Johns Hopkins Hospital during Dr. Hurd’s long vacation. This position he filled ably and efficiently; and, on Dr. Hurd’s return, he was appointed Assistant Superintendent of the institution. Here he soon made himself felt, not only in his administrative

capacity, but as a valuable helpmate to Dr. Hurd in the literary work connected with the position. In recent years he had published several thoughtful communications on subjects pertaining to hospital management, and his opinion and advice were beginning to be more and more widely sought. On Dr. Hurd's retirement, the editorship of the BULLETIN and the *Hospital Reports* fell on him. His services in this capacity were invaluable. His patience, his conscientiousness, his literary ability, his unfailing good taste, were relied upon by all. We had looked forward longingly for the day when we might have a library worthy of the hospital, in which Norton might find his proper position as director of the literary functions of the institution. It will not be easy to find his successor.

And during this time he has grown into our hearts as few men could.

After long years of tried and devoted friendship, Norton was married but twelve months ago, to Miss Cæelia Hendrickson, of Frederick. No union could have been happier or more complete. How pitiful was its brevity!

How little, sometimes, can we measure a man's work in the world by his contemporaneous fame or by the permanent monuments which bear his name. Norton was not widely known, and he published little; but he did a good work, and he leaves many friends to whose lives he has added something uplifting and enduring. Only now that he has gone, do we who knew him begin to realize how large were his generosity and his charity, and how deep had been his influence upon us. But no one who knew him well, failed to realize at all times the unusual quality of his friendship, a friendship which meant not only perfect loyalty and devotion but other responsibilities not easy to fulfil, to which he was ever true. He who was blessed with his friendship never failed to receive, when it was needed, the kindly and just and direct word of warning or criticism so hard to give but so wisely and simply and considerately offered. His friends' honour and reputation were as dear to him as his own. For these friends, and they were many, he has done a noble and a lasting work. His memory will forever rest in their hearts, and through their better lives his influence will long endure.

When we look back upon his career, we shall remember his simplicity, his modesty, his upright, uncompromising honesty of purpose and word and practice, his delicate charm of mind, his varied attainments and interests and abilities, his faithful work in many capacities; but above all we shall remember the rare beauty of his friendship.

WILLIAM S. THAYER.

DR. OTTO GUSTAF RAMSAY.

The Faculty of the Yale Medical School places on its records this minute concerning Dr. Otto Gustaf Ramsay, whose death took place on Friday, June 12, 1914.

Otto Gustaf Ramsay received the degree of Doctor of Medicine from the University of Virginia in 1890, at the age of twenty. During the latter part of 1890 and the early part of 1891 he spent some time in postgraduate work at the College

of Physicians and Surgeons, New York. In the fall of 1891 he worked in the medical dispensary of The Johns Hopkins Hospital, and in the summer of 1892 served as resident at the Garrett Children's Hospital. In the fall of 1892 he entered The Johns Hopkins Hospital as an interne on Professor Osler's staff, and served in this capacity for eighteen months. He then received an appointment on the Gynecological staff under Professor Howard Kelly, but left in the fall of 1894 to take charge of Dr. Kelly's private hospital, which position he held for about a year. During 1895 and 1896 he spent a year in Germany, working with Ziegler in Freiburg and visiting the important clinics. From the fall of 1896 till 1898 he was on Dr. Kelly's staff again, part of the time as resident. He left the hospital in 1898, but continued his work with the department as Instructor in Gynecology. He came to Yale in 1900 as Professor of Obstetrics and Gynecology, which position he held until his death.

Otto Ramsay was a man of strong personal charm. He was by nature genial and sympathetic, and inspired in his colleagues, his students and his patients a real and lasting affection. His personality, his great natural ability and his broad training in his chosen field, all served to make him what he was: a successful teacher, a thorough practitioner, and a man whose sympathies were always enlisted in the cause of the best ideals of his profession. With all this, he was extremely modest and unassuming. In his early professional life he found time to contribute to the literature of his specialty; but in his later years he was so driven by the exactions of a large practice that he seldom wrote, a fact which he not infrequently mentioned with regret. Through all the strenuous years which marked the close of his career he still, however, retained his academic sympathies.

Those of us on the Faculty who were associated with him will always look back on his useful and honorable career with the feeling that it was indeed a pleasure and a profit to have been associated with such a man.

(Signed) W. H. CARMALT,
H. B. FERRIS,
GEORGE BLUMER,

Committee.

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PROCEEDINGS OF SOCIETIES.

JOHNS HOPKINS HISTORICAL CLUB.

Special Meeting, May 26, 1913, in Memory of Dr. John Shaw Billings.

The meeting was called to order by the president of the club, DR. HENRY BARTON JACOBS, who spoke as follows: This meeting has been called as a special meeting of the Historical Club, so that we here may join with other parts of the country in paying tribute to one whose influence has been so pre-eminent in this institution. In the beginning, his voice and his influence were most material in forming this hospital, and so as a tribute to him, we have met this evening. Dr. Hurd will open the exercises.

DR. HURD: I have always regretted keenly that I did not make memoranda in order to preserve in detail many interesting reminiscences which Dr. Billings from time to time gave of his early life.

He once informed me that he came of New England stock and that his parents were pioneers at the West; he being born in Indiana. I have an impression that his family removed soon after to Ohio, and I know from many things which he said that his early life was one of hardship, privation and considerable struggle.

He worked his way through college and later gave many interesting details concerning the privations which he endured. On one occasion, owing to a change in text-books—when he found himself under the necessity of spending, what seemed to him, a large sum for new text-books, an expenditure which had not been foreseen—he debated whether he should sell his overcoat or his undercoat, and finally parted with the latter, and wore his overcoat instead. The arrangement proved a judicious one until the warm weather of summer came, when he experienced more or less inconvenience from the heavy garment, and its manifest lack of suitability to summer wear.

He also spoke of the extremely plain fare which he prepared himself, generally cornmeal mush and milk (oatmeal not being then in fashion), and what he called "papered" eggs. He used to describe with considerable humor the details of cooking an egg upon the top of the stove upon a sheet of paper. The egg, if carefully watched, could be relied upon to cook sufficiently before the paper burned through; if, however, the cook became absorbed in literary matters or his attention was diverted, there was always danger that the paper would burn through and the egg would be spoiled. He always claimed that he attained great success in thus cooking an egg, and learned to do it to perfection.

In an address which he delivered at a commencement at Miami University, Oxford, O., he gave interesting details of his college life. His education seems to have been largely acquired by himself, and was not due to any great advantages for study or to special scholarly surroundings. He learned to use books, and to acquire knowledge. I know little or nothing of his medical school education, or of his hospital experience, prior to entering the army, and must leave these matters to

others. Others also will probably give details as to his army life and his work as a bibliographer and sanitarian.

I am asked to say something of his services to the Johns Hopkins Hospital in its plan and construction. I have always believed that his most eminent services to the public were associated with the plans, construction and organization of the Johns Hopkins Hospital. I have recently had occasion to look over the series of five essays prepared for the information of the trustees of the hospital at the suggestion of Dr. Billings, and afterwards edited by him. These essays were written by Dr. Norton Folsom, at that time superintendent of the Massachusetts General Hospital, and an able hospital planner; Dr. Jos. Jones, of New Orleans, who had much experience as a sanitarian, medical writer and active hospital manager upon the Confederate side during the late Civil War; Dr. Caspar Morris, a retired Quaker physician of Philadelphia, whose work had been largely in diseases of children; Dr. Stephen Smith, still living at the advanced age of ninety-one years, who had shown versatility in medicine and surgery, as well as in administrative work such as hospital planning, inspection, lunacy administration and the like, and finally Dr. Billings whose services had been secured by the trustees because they wished to preserve as far as possible the experience which had been derived from the construction and administration of the hospitals of the United States Army during the Civil War. Each of these gentlemen prepared plans for the future hospital, and accompanied his plans with a description or an essay upon some branch of hospital construction, organization, or management. It is evident from a study of the plans originally prepared by Dr. Billings, that while they were in all respects superior to the others, they were much modified before the buildings were constructed. He originally favored buildings of at least two stories in height, and spoke of elevators and other arrangements for convenient administration which were later esteemed extremely heretical. When I came to the Johns Hopkins Hospital I was informed by the president of the Board of Trustees that the subject of elevators had been settled for all time, and that under no circumstances would the advisability of putting elevators into any one of the buildings ever be considered. It is evident from comparing the plans which were finally adopted and the original plan which Dr. Billings prepared that there had been a progressive evolution in his mind of the present plan, due probably to the study of other plans and his journey to Europe to perfect him. He always had an open mind, and sought counsel from experts. He further had the rare faculty of acting upon the essential part of another person's plan, and was able to modify it and to make it a part of his own, to the mutual advantage of both.

In 1877 he accepted the position of medical adviser to the Building Committee of the Board of Trustees, which really signified an arrangement by which he and the president of the board, Mr. King, were to plan and build the hospital.

The wards were to be built on the single story pavilion plan. This decision undoubtedly came from his experience in the

army hospital largely due, it seemed to me, to the general impression at that time—which we now know to be erroneous—that much disease was caused by miasma and malaria, which had their origin in emanations from the ground; hence, in all his plans, he decided to leave the basement unoccupied by patients and arranged also that wherever there was any communication between the basement and the first story, such as by flues communicating with radiators in the basement, even when they conveyed hot air, a thick coat of asphalt should be spread beneath them so that the floor might be wholly impervious to any exhalations from the soil.

He also made every provision against infection and contagion. No elevators were permitted in the buildings because of the danger of communicating infection from one story to another.

He also insisted upon perfect ventilation, not only by natural currents of air introduced from without, but also arranged for the removal of impure air from apartments by means of exhaust fans, and high shafts, with accelerating coils. He had a great desire to make everything perfect and no building up to that time, or since, had more enlightened arrangements for fresh and pure air, or more perfect construction of apparatus for heating and ventilation.

In the light of our present knowledge of hospital construction, the plan of his buildings is open to certain criticisms. The whole structure was too much upon the line of the army hospital. It was deficient in modern facilities for nursing and in the modern laboratories for studying disease. The sink rooms, ward bath rooms, linen rooms, etc., were too small, and not arranged for the convenience of nurses. They seemed to contemplate the presence of the army orderly at every turn. There was also imperfect provision for housekeeping and store rooms and other conveniences, which housekeepers love to plan and sometimes to use. The operating rooms were also inadequate and not sufficiently studied in the light of the present demands of modern surgery. These were minor defects and were incident to the times and not to any oversight on his part. There is no question, but that his plans influenced hospitals in a way unparalleled in the history of hospital construction and that he gave a tremendous impetus to better hospitals, by directing the attention of medical men, sanitarians and others to the absolute necessity of certain great essentials, viz.: more perfect ventilation, and heating and the prevention of contagion.

In my relations with Dr. Billings, which at one time were fairly intimate, although of late years I saw little of him, I was always impressed with certain characteristics which stand out prominently in my mind.

He selected those things which it was essential to do with unerring instinct, and did not waste his time over unessential matters. This was evidenced in all his writings. I do not think that he ever polished his sentences or modified his original draft of any paper to any great extent. He set down in plain English the ideas which came to his mind, and they were usually so well considered and so self-evident, as to commend themselves to all who read what he wrote.

He had great quickness of decision, and did not waste his time in making and unmaking plans, but planned quickly and readily and then dismissed the matter from his mind. I remember when I was associated with him in the Chicago Hospital Congress of 1893, he gave me the names of certain physicians from abroad who ought to be invited to contribute papers, and the subjects of their papers, sketched out hastily upon a blank piece of paper while he was making the journey from Washington to Baltimore. Every detail was carefully considered, and from that draft it was possible to send out the invitations and to arrange that portion of the program. I doubt whether he ever gave it any more consideration.

He had a rare knowledge of human nature, and a certain dry humor which gave him great influence when he presented his views upon any subject. He was broad-minded and liberal; kind-hearted to all people and interested in their welfare. His face invited confidence. I remember on one occasion he told me that he had recently been approached by an ignorant market woman with a letter in her hand which she was unable to read. She asked him to step aside into a secluded corner in order that he might read aloud a letter from a wayward son. He found upon reading it that her son was in prison and that his mother fearing such to be the case, had not ventured to show the letter to any of her friends or acquaintances in the market, but had waited for a person in whom she felt she might have confidence that he would preserve her secret. She had selected Dr. Billings to read it, although an absolute stranger, because she saw at a glance that he would be worthy of her confidence.

Dr. Billings had, however, a certain intolerance of fools and was impatient of them in a manner which sometimes interfered with the success of his wise plans. He was too busy to waste his time in useless talk or windy argument and hence sometimes spoke his mind dogmatically and too plainly for his own good. I have always believed that had it not been for influences which came from politicians and others whom he had wounded by such praiseworthy intolerance, he might have been surgeon-general of the army.

He had rare powers of continued labor and by dogged perseverance accomplished wonders. I have never known a man who did so much work with so little friction and who brought things to pass so satisfactorily. I remember when he was preparing the Index Catalogue, that while much of the skilled work was done by trained experts and much of the unskilled work was done by unskilled labor, which he had been able to secure, instruct and direct—the last revision of it came under his own eye, and he read the manuscript of the Index Catalogue, volume by volume, and so complete was his revision, that in one volume of nearly or quite 1000 pages, the cost of changes in page proof was a little more than thirteen dollars! Could there be any better testimony to the industry, accuracy and scholarly attainments of the man?

He was above all a true friend, interested and unselfish, a loving husband, a kind father and a good son.

His life was a most active and energetic one up to its very close; only a few days before his death, I had the satisfaction

of meeting him at dinner, and was impressed with the vigor of his mind and his broad sympathy with and interest in every branch of knowledge.

COLONEL McCRAW: I am somewhat at a disadvantage compared with the other speakers to-night, in that I never had the inestimable privilege of working with Dr. Billings, or of being intimately associated with him. I met him when I was a youngster in the army and looked up to him with all reverence as one of the great men of the medical corps. I also visited him at his house in Georgetown. I am glad to say that at one time he made an application for me to come to Washington to learn the business of the library and museum under his tutelage. I think it was his idea to get a number of the younger officers detailed in Washington in succession to learn something about the work of the museum and library, so that when he gave it up, there would be several from whom to choose his successor. Unfortunately, this plan was not carried out. The Secretary of War would not consent in my case to make the appointment, and so I missed a great chance of preparing myself for the position I now hold. In his later years, when Dr. Billings visited Washington, he always came to the library to see his old friends, he spoke to all of the clerks and went in for a chat with his old friend, Dr. Fletcher. He generally honored me also with a short visit. He was always sympathetic, always had valuable advice to give and maintained to the last his interest in the library.

Living as I do in the institution which he built and in the midst of that great garden of medical literature which he planted and tended, I am amazed more and more every day at its completeness, its great scope, its catholicity and at the fact that nothing whatever connected with the literature of medicine has been neglected. It is not only the works of the masters of medicine—the great men of the profession—that appear there, but every irregular, every quack who has in any way written on the subject of medicine is represented in the library of the surgeon-general's office. It was Dr. Billings' idea that nothing whatever connected with medicine should be neglected, but that *all* should be collected and catalogued.

Dr. Billings was preeminent in everything. I think there is no doubt that whatever career he had undertaken he would have succeeded in it. He undoubtedly had the making of a great soldier. He would have made a great general. He would have made a most able prime minister, and he would have had his own way. He would undoubtedly have made a great ruler, probably an easier position to fill.

When he entered the service at 24, he came to Washington and appeared before the examining board, the last candidate to present himself. The board thought it was over with its labors and had made up the merit roll of the candidates, when the order to examine Dr. Billings was issued. The members of the board very soon found out that he was going to pass, and they also found out very shortly that he probably should be ranked first on the merit roll. So much to his dismay, after he had finished, as he thought, the examination in all the subjects set, after a consultation among themselves, they returned to

anatomy again and began all over. Their idea was that they wished to be perfectly fair to the man who had already been ranked first upon the list, and they put to Dr. Billings all the questions they had asked him, in addition to those he had already drawn. As the result, Billings came out first in his class. He said that at that time he had three things which were novelties to the physicians in Washington. He possessed a hypodermic syringe, a set of clinical thermometers and a Symes staff. The possession of this last, and the fact that he had some skill in using it, led Dr. Tripler to give him as one of his first tasks, a series of operations upon strictures in old soldiers in Washington, old men valuable to the government at that time, and who would otherwise have been discharged and their services lost.

Very soon after this, almost immediately after being commissioned, he was given charge of Clifton Hospital in Georgetown, where he had under him several contract surgeons and 60 sisters of charity. He received there about 750 wounded from the seven days fight before Richmond, both Union and Confederate. He did nearly all the surgery, as he was practically the only operator at this hospital. It was here he did the first exsection of the ankle joint. A perfect recovery took place.

From Clifton Hospital he went for a short time to Philadelphia and then joined a regiment in the Army of the Potomac in time to be present at the battle of Chancellorsville. At Chancellorsville he was made an operating surgeon in the division hospital. He had there the most difficult problem that can be given to a medical officer in the field—that is, the care of the wounded and their carriage to the rear in the case of an army which is itself falling back. He chose two cottages [one of them the Chancellor house] in succession for his hospital. He was driven from both by brisk shell fire and finally had to take to the woods with his wounded and treat them under improvised shelter. At that time operation on the field was looked upon as a necessity. Nowadays the problem would be to dress as quickly as possible with the early aid packages and evacuate the wounded to the rear and so get them out of the way. At that time, however, it was considered necessary to do a great amount of operating on the field. Dr. Billings seems to have been a most successful and very able operator. Indeed he managed, even at Chancellorsville, to do a number of major operations, including gunshot wounds of the skull with injuries to the brain.

His next appearance was in the Gettysburg campaign. At Gettysburg he had his hospital established in a large house and barn on Round Top. When he rode up to take possession of this building, he was saluted by a volley from the enemy nearby. He found that the place had just been deserted by the occupants, fires were still burning, bread was ready for baking and water was boiling. He took charge of the wounded there without loss of time. Round Top did not prove a wholesome place for a hospital. In a short time he was driven out by brisk fire, and had to improvise a hospital in the shelter of the woods. This time the army was not retreating and he remained in this hospital about three weeks. He reported that

his wounded at this place did remarkably well, and the reason given is characteristic. He said: "They are in the open air, they have plenty to eat, they are being washed by a clean, warm rain and we have no flaxseed." His scepticism regarding the soothing flaxseed poultice and its value in "drawing" pus from a wound was ahead of his times, and in this also he proved himself a "progressive."

After Gettysburg, he was ill for a week or two, and from sick leave reported for duty around New York, and was in several of the large hospitals there.

At Spottsylvania, he was attached to the medical director's office of the Army of the Potomac, to which he was sent for the purpose of gathering statistics and data concerning the medical operations of the Army of the Potomac. His reports as medical inspector were full of valuable suggestions, both as to medicine and surgery and as to military administration.

He came to Washington in 1864 and was assigned to duty in the surgeon-general's office, and on that duty, in one position or another, remained until he retired in 1895. The first five or six years of his service must have been very arduous. It is simply unrecorded drudgery. There is no minute record kept of the duties of an officer in a war department bureau, but these years must have been the most arduous of his life and, no doubt, among the most instructive. At any rate, he learned the ins and outs of government business from the beginning. He became acquainted with the manners and customs of comptrollers and treasurers. He knew the ways of Congressional committees, and was forming himself for the leading position that he soon took. He had charge of the disbursements of the hospital division, a most important task. He had charge of everything connected with the department of contract surgeons, of whom there were a great many at that time. He had charge of the organization of the veteran soldiers, a duty which required much medical knowledge. Altogether his work was of great importance. While in the office, he came in charge, a duty which he assumed for himself I suppose, of what was fondly called the library of the surgeon-general's office. This library in 1864 consists of a couple of large bookcases, or sets of shelves, with perhaps 1000 books. I have a catalogue of those books, which I sometimes show, as an object lesson, to people visiting the library. It is a little, very little pamphlet, with some of the titles in pen and ink and only a few printed. Even at that time, I suppose if those books had been handed over to an old book dealer, they would have been at once put out on the pavement and marked, "Any book on this table for 10c."

It seems to have always been his desire to establish a library and to index it properly. In fact he states that "the establishment of an adequate library for American teachers and physicians, with a reasonably good index, so that these people could, instead of reading over the indices of thousands of volumes in different places, obtain what they wanted in one," was his fondest aspiration. How well he succeeded and how far he surpassed his original aspiration, everyone who now knows the library can tell. We still carry on the institution along the lines that Dr. Billings laid down. We have not

modified very much the routine method in which the material is cared for, in which it is indexed and in which it is loaned all over the country. The foundation that he laid, we rest upon still, and we try to carry on the institution as he would have carried it on.

From the thousand volumes in 1864, the library has now grown to half a million and a little over. There have been indexed over a million and a quarter titles of books, pamphlets and articles in periodicals. Eight thousand different journals alone have been indexed in the library, of which we still subscribe to a current list of about 1400. The institution far from being a "reasonably good library for the use of American physicians," is known all over the world. Through its catalogue, it is used almost as much abroad as it is here, and there is hardly a college, a university or a learned society in the country that has not at one time or another come to us for assistance.

All the time he was building up this monumental institution he seems never to have lost an opportunity to take part in any question affecting public health and welfare that came before him, and in every one he seems to have been preeminent. He made for two censuses, the tenth and eleventh, valuable reports on the vital and mortality statistics of the United States; he took a prominent part in fighting the epidemic of yellow fever at Memphis; he took a prominent part in the construction of the Johns Hopkins Hospital; and three or four other hospitals are largely due to his interest and the experience he had in hospital construction. He wrote an excellent history of surgery—Dr. Garrison thinks it the best history of surgery in English, a valuable paper on alcoholism, a treatise on ventilation and heating and innumerable papers and addresses. From his writings could be culled a little book of extreme value, of wit and wisdom—the kind of wit that does not grow stale, the kind of wisdom that helps every man because it is practical common sense. A few of his sentences one cannot but remember. His instructions as to the best way of writing a medical article are more valuable to a young writer than the reading of many essays and treatises. They were: First, have something to say. Second, say it. Third, stop when you have said it. Fourth, get a good title. The nearest approach to this is to be found in the matchless advice given by Humpty Dumpty to Alice, when she was giving him the history of her life. She asked: "Where shall I begin?" He answered: "Begin at the beginning, go on to the end, and then stop."

One extract from his presidential address before the Philosophical Society of Washington, December 4, 1886, I will read, as it is in a different vein from the others:

The old creeds are quivering, shifting, changing like the colored flames on the surface of the Bessemer crucible. They are being analyzed, and accounted for, and toned down, and explained, until many are doubting whether there is any solid substratum beneath; but the instinct which gave those creeds their influence is unchanged. . . . When we examine that wonderful series of wave marks which we call the spectrum, we find, as we go downwards, that the vibrations become slower, the dark bands wider, until at last we reach a point where there seems to be no more movement; the blackness is continuous, the ray seems dead. Yet

within this year Langley has found that a very long way lower down the pulsations again appear, and form, as it were, another spectrum; they never really ceased, but only changed in rhythm, requiring new apparatus or new senses to appreciate them. And it may well be that our human life is only a kind of lower spectrum, and that, beyond and above the broad black band which we call death, there are other modes of impulses—another spectrum—which registers the ceaseless beats of waves from the great central fountain of force, the heart of the universe, in modes of existence of which we can only dream.

He has passed beyond that dark band himself and the world is darker for his loss.

DR. JACOBS: Since Colonel McCaw began speaking, Dr. Garrison has come in. I am wondering if he may not supplement Colonel McCaw's remarks.

DR. GARRISON: I have very little to add, but I have a very interesting picture of Dr. Billings which I should like to show you. A boyhood chum of Dr. Billings' son once told me a very characteristic thing about the doctor. The two boys had a chemical laboratory in the Billings home, and one time during their experiments they had an explosion, almost blowing out the side of the house. They were somewhat alarmed, but when the doctor came in and heard of it, he said absolutely nothing. He went in to his dinner and the thing passed off without any disturbance at all.

He cared absolutely nothing about the foibles of people, their little peculiarities, so long as they were doing their duty. He was always exacting about work. He was exacting of himself and exacting of others, as people of stern character are. Once there were two young fellows wrestling in one of his office rooms at lunch time. Dr. Billings had occasion to go that way on business. He peeped in, saw that they were wrestling, and then simply shut the door and waited until they got through. He then went in as if nothing had happened.

My relations with him were entirely official. I was never at his house but once, and at that time after 9 p. m., I found him piled up with books at work, as Dr. McAllister has described in the British Medical Journal. In my relations with him, I always found him an absolutely fair-minded, generous and courteous gentleman. I never had any difficulty with him myself, and I don't think any of the men about him had. They were devoted to him and his work. I mention these things, because I have sometimes heard Dr. Billings referred to as hard. That was because he was exacting, but as I have said, he was more exacting of himself than of anyone else. He worked for the government all day long, and as I happen to know, very often nearly all night long.

DR. JACOBS: Dr. Norton knew Dr. Billings and I think you would all be interested in some of the personal details which he can give us.

DR. NORTON: I wish that I had known Dr. Billings better than I did. My friendship with him began years ago when I first came to the hospital and made the acquaintance of his son, then an interne in the hospital, who has been my friend ever since. My esteem for Dr. Billings grew as I came to know him more intimately. The last time I saw him was a few

weeks ago at a dinner given to him by Dr. Weleh. He was always interesting, and at this dinner most interesting. I think it is strange, considering how able he was, that he was not more widely known to the profession at large in this country. His friends, of course, knew his large powers, but he had none of that United States reputation that some men of much less worth and ability have. He was a modest man, but rightly knew his own worth and let others learn it by observation of his character and deeds, for he never boasted. He was a man of large frame, vigorous and soldierly. Agreeable and pleasant when you met him, he was easy to get along with, like so many men who have had to make their own way, and rub up against others and against the roughnesses of life.

Dr. Hurd has said a good deal that I was going to say. If I had written my paper, it would seem exactly as though I had copied it.

Dr. Billings was a good judge of men, and he did not judge them easily. He wanted to get out of men something that was worth while, and so he did not have any patience with those who were triflers. I think this came from his having made his own way, which he had to do largely, since as a young man his means were very small. This usually makes men severer in their judgment of others. But with him, it was not unkindness. He never said unkind things of anybody. One felt perfect security and confidence in him if one went to him for help. He was the confidant of many older men than myself. His son John tells me he has found out since his father's death that many men, more or less his contemporaries, went to him and confided in him on all sorts of questions. This shows the nature of the man.

I thought, as Dr. Hurd has said, that he was a man of quick judgment, that he must have been, but again I have learned that such was not the ease. When you went to him for advice and oftentimes got a prompt reply, and wondering at his quick reply, probably asked him how he had come to form his opinion, he would refer to something that might have occurred some weeks or months earlier, which showed he had been thinking of this thing for some time. So it was not any coarseness on his part at all in forming his judgment, which was always sound. One might not always agree with him, but he always had good grounds for his opinions. At the same time a man so capable as he was must have learned to use his mind quickly and with readiness and be able to pass judgment without hesitation; and he could do that.

As Colonel McCaw has said, he would have been a power in anything he undertook. I have often wondered if he might not have put through the Panama Canal, which Colonel Gorgas has done. He picked out his assistants well, and they were devoted to him, because of his loyalty, his readiness to help and his justice. I know there was one old colored servant in the family, whom he had had for forty years, who was devoted to him heart and soul. It may be said this is a trait of the race, but it speaks well for the master. Dr. Billings was a quiet man; there was never any bluster about him. He went ahead and worked, as we say, like a Trojan. He was thinking constantly, but was able to lay aside his worries when he went

me and to spend the evening reading novels. He was a tremendous novel reader. I doubt if any reader in America has read as many novels as he did, although he only read them as a recreation. Newspapers he did not care for, simply glancing over them in the morning. He had a very remarkable memory, as a man able to organize must have. He could not have compiled such a library as he did in Washington without having an extraordinary memory. He was in a sense retiring. He never appeared a great deal in public, although he was called to meet scientific men, but I don't think he cared much for ordinary society. He was simple in all his tastes, and there was no affectation about the man. He was just a fine, strong man. Anyone who met him, could not help but feel that he was talking to a man of unusual powers and strength of mind.

DR. JACOBS then introduced Dr. Halsted, who spoke as follows:

DR. HALSTED: It is merely as a friend of Dr. Billings that I shall speak to-night at this little gathering, realizing that I can add nothing to what has already been said in praise of his character and marvelous achievements. Recollections of my first introduction to Dr. Billings in 1887 are still vivid, for I realized that I was under inspection at the intimate little manner which Dr. Welch had arranged for the three. During this and the following year Dr. Billings would occasionally drop into my room at the pathological laboratory to say an encouraging word or to discuss some of the problems connected with the surgical department of the hospital and university.

In the organization of the dispensary, with which I was entrusted, I frequently sought his valuable aid. It was at his suggestion that the card index was introduced in the dispensary, where its value was so convincingly demonstrated that subsequently it was adopted in the hospital; and he found in me a trained man who remained a year to assist in inaugurating the system, which was new for hospitals.

In this hospital so admirably planned by him, no special provision for surgery was made by Dr. Billings. He enjoyed emphasizing this intentioned omission and making the comment that inasmuch as no two surgeons would be likely to have the same views as to what the ideal operating room and its accessories should be, it would have been a hopeless task to attempt to satisfy the then unselected director of the surgical department.

I shall never forget his words or his look as he said to me after I had been told of my appointment, "Now you have the ball at your feet, all you have to do is to kick it." I understood his friendly, almost fatherly smile to say, "I am not quite sure that I approve of you altogether, but you may count upon my support." Since then he gave me many proofs that I had not misinterpreted his kindly glance.

Soon after the opening of the hospital Dr. Billings became a patient within its walls. One day as I was removing a subcuticular stitch of silver from his wound he protested, saying that the pain was considerable and that hence the procedure could not be ideal. I replied that we were experimenting with

a new form of suture and had not as yet determined the proper time for its removal. "Oh, very well," he said, "go ahead, I can stand a little pain in a good cause." Once or twice he invited me to his home in Georgetown. I would join him at the surgeon-general's library and find him stuffing his overcoat pockets with journals and clippings. These he would take home with him every night and index before going to bed. He explained that these were details in connection with the indexing of the catalogue that he felt should be attended to by himself, and added, "If others see that I give careful personal attention to these matters they will realize that it must be worth their while for them to do the same."

Since then when oppressed by the seeming magnitude of one of my little anthills of work I have recalled the advice of Dr. Billings: "Devote a small amount of time each day to it and the mountain will melt away with astonishing rapidity."

The last time I met Dr. Billings was a few months before his death. We were traveling from New York to Baltimore and dined together on the train. His mental vigor seemed undiminished and his interest as keen as of old in his plans for the future of the various institutions which were guided by his masterful and dominant hand.

Dr. Billings was too great a man to be fully appreciated in his time.

The monuments of work which he has left are records the value of which cannot be estimated by the many, possibly by none; and the debt which others owe him for stimulus and suggestion can never be summed up.

Dr. Thayer was then asked to speak.

DR. THAYER: I well remember the first time that I saw Dr. Billings. It must have been something over twenty-five years ago when he delivered a series of lectures on the history of medicine at the Harvard Medical School. A valued teacher had told us that Dr. Billings was one of the most distinguished figures in American medicine, and even then, as a second or third year medical student, I had an almost reverent admiration for him as the editor of the Index Catalogue, and the Index Medicus.

I remember his appearance at that time. His tall, dignified, commanding figure, his impressive, forceful manner, his evident mastery of his subject left with us an impression which few have forgotten.

And then I remember vividly the first time I had the pleasure of meeting him. A few years later, while visiting in Washington, a warm-hearted and kindly, but highly eccentric lady, the wife of a retired army officer, who had known Billings as a young army surgeon, I was invited by my hostess at a late hour one evening to pay him a call; and so we set forth for Georgetown. It must have been about ten o'clock at night when we arrived at the door. No lights were to be seen. Evidently all had gone to bed. Undaunted, however, my good hostess rang the door bell. There was no answer. She rang a second and then a third time. Finally, the window over the door was opened, and Dr. Billings appeared in his nightgown. "Dr. Billings," said my companion, after

announcing herself, "I am afraid you have gone to bed." "Oh, no," he replied, "not at all, I will come down in a minute." "But I am sure you have gone to bed," answered the good lady. "Not at all," said he. "If you will wait a minute, I will come down at once." But my companion insisted, and compromised in the end by introducing me from the doorstep, in a voice, which I fancy, must have been audible for two squares. It was an impressive introduction in which the names, character and achievements of my ancestors for several generations were carefully recounted. At the conclusion of the address, it was requested that Dr. Billings name an hour on the following morning at which I might present myself at his office in the library.

The next morning, a shamefaced and embarrassed youth appeared at the surgeon-general's library, where he was received by Dr. Billings with a simple, kindly courtesy which he has never forgotten.

In the early years of this hospital, Billings was a frequent and welcome visitor, and all were familiar with him at his home in the library, that great library which is the Mecca of all American physicians.

What a work it was that he did in the foundation of that collection and what an undertaking was the Index Catalogue! It is impossible to estimate the debt of American medicine, the debt of the whole world to this man.

It has been said, and I believe justly said, that one of the most characteristic features of the scientific work of the American medical student is the completeness of his bibliography, and the familiarity shown by the author with the literature of the world relating to his subject. And how many realize that this is, after all, due in great part to the circumstance that Dr. Billings in that great library which he has built, that library which is so freely open to all, has accumulated an unexcelled collection of the widely distributed medical literature, and in the Index Catalogue and in the Index Medicus has given us a ready means of reference to this vast storehouse.

Twenty years ago, one of my friends, while in Munich, called upon his old teacher, Professor von Pettenkofer. Entering his library and turning towards his bookshelves, the old professor, with a sweep of his hand towards the Index Catalogue said: "That is the greatest work in my collection." I recall another incident which illustrates that which the Index Catalogue means in all parts of the world. In 1893, while looking up some matters in the *Bibliothèque de l'école de médecine*, I sent to the desk a slip calling for a number of the then new *Archives des sciences biologiques de St. Petersburg*. The attendant handed it to the librarian on duty without comment. I observed his proceedings from a distant corner of the room. He looked at the reference for a minute, seemed puzzled, then turned and took from the shelf the last volume of the Index Catalogue which contained the title of the first volume of the series. Unfamiliar with the journal, his first thought was to search for it in our Index Catalogue.

Such a work as the Index Catalogue could have been accomplished only by a man of immense capacity, of extraordinary power of organization. These qualities Dr. Billings had.

Whatever he undertook, the perfect implement seemed to spring to his hand; wherever he went, as if by magic, the most efficient co-workers surrounded him so naturally, so simply, so inevitably, that one might almost have fancied that it was the work of the hand of chance. But those who knew him saw in this grave, strong man, the mind of a master.

Where shall we look to-day for such breadth of conception such an activating spirit!

None should revere the memory of Billings more than we for this hospital is his child, and few realize what we owe to his wise counsel in the days of its infancy. We, the guardians and the offspring of this child of his, must see to it that his name is perpetuated among the buildings which he designed by a memorial worthy of the man. Here, of all spots, there ought to stand a dignified edifice which should bear the name "The Billings Memorial Museum and Library," which should gather together the scientific collections and the books from the hospital and the medical school, which should offer here near the greater foundation in Washington, ample opportunity for the study of the history of that art to the service of which this great man so nobly devoted the major part of his life. Such an institute would be a fitting honor to a noble memory.

But, alas, it can never give to those who follow us the memory of the man which is ours—the dignity of his presence, the firmness and gravity of his speech, that rare sense of poise and balance and power which he impressed upon all who approached him. It was good to have seen and to have felt all this. Something, to be sure, is preserved in the beautiful portrait by Cecilia Beaux, but it is a sadly small part of what we who have known him could wish to transmit to those who shall follow us.

Dr. Winford Smith, the superintendent of the Johns Hopkins Hospital, was next introduced.

DR. SMITH: I cannot speak of Dr. Billings as one who was privileged to know him personally. It has been my regret that I was not so favored. Of Dr. Billings as a student, a scholar, a physician, and an organizer, others have spoken.

Dr. Billings was so long associated with this institution he did so much for it, his judgment was so sound and the principles which he helped to establish have had such far-reaching influence, that I wish to recall on this occasion certain thoughts of his as expressed in his address on the occasion of the opening of the Johns Hopkins Hospital, nearly a quarter century ago. Dr. Billings said:

The third principle to be kept in view, in such a hospital as this is that it should provide the means of giving medical instruction for the sake of the sick in the institution as well as out of it. It is well known, to those familiar with the subject, that the sick in a hospital where medical instruction is given receive more constant, careful and thoughtful attention than do those in a hospital where no such instruction is given. The clinical teacher must do his best; keen eyes will note every error in diagnosis every failure in results of treatment. Moreover, the very act of teaching clarifies and crystallizes his knowledge; in attempting to explain, the dark places become prominent and demand investigation: and hence it is that those cases which are lectured on receive the best treatment. I need say nothing here

On the other side of the question, the value of properly trained physicians to the community and the necessity for hospital instruction in such training. . . .

Closely connected with this subject of teaching is that of increasing our knowledge of the causes, symptoms, results and treatment of disease, in fact one cannot be thoroughly well done without the other, and hence many of the provisions for the one are also useful for the other. . . .

One structure is very largely devoted to and fitted for experimental research, and that is the pathological laboratory, where the causes, processes and the results of disease are to be studied. Upon the results obtained in that laboratory may yet depend the saving of many lives; the relief of unspeakable agony, the warding off of pestilence from the city, and, to put it in a strictly business light, the value of real estate and the rate of taxation of this community. We are on the verge of great advances in our knowledge of the causes and methods of disease, and I feel sure that these will be only preliminary steps to far greater and better knowledge of how to prevent them or to treat them than we now have. The probable length of life of the new-born infant to-day is not much more than half what it ought to be, the practical productive period of life of our men and women is shortened and interrupted by unnecessary disease and suffering; but remember, if these things are to be amended it is not merely by teaching old doctrines—we must open fresh windows and let in more light, so that we can see what these obstacles really are. It is in this work of discovery that it is hoped that this hospital will join hands with the university, and it is in this hope that some of the structures around you have been planned and provided.

Whenever and wherever the problems of higher medical education have been discussed within the last ten years, there has been speculation as to the probable course of the Johns Hopkins Medical department, and the influence it would have upon the standard. . . .

What is it then that the physicians want? Is it more physicians, more family practitioners, more surgeons, more specialists? They know very well that there is no danger that the supply will not be equal to the demand: when they become overburdened with practice, they do not at present find it difficult to obtain assistants; they have no fear lest the seventy or eighty medical schools of this country should fail to produce a sufficient number of medical practitioners to meet the wants of our increasing population; and they know also that the medical schools of Great Britain and Germany are sending to us quite as much of their product as we can conveniently dispose of. They hope that the Johns Hopkins Medical School and Hospital will do two things. The first is, that it will demand of those who propose to become students, evidence that they have sound basis of preliminary education before they commence, and that its standard in this respect shall be little below that of the requirements for granting the degree of bachelor of arts in the university. It is hoped that the men thus selected will go through a carefully graded course of study, including actual work in properly fitted laboratories and that after this they will be brought into contact with the sick and thus obtain practical experience of the duties and responsibilities of the practitioner of medicine before they offer their services as such to the public. . . .

In this country medical schools have either had no connection with universities, so called, or the connection has been slight and nominal, such as depends upon the formal conferring of degrees by the university. Here, however, through influence of the biological department, there are secured common interests and mutual influence, and it is hoped, therefore, that the necessary details of technological instruction will be arranged in accordance with and subordinate to the broad principles of scientific culture upon which this university is organized.

It is because it is believed that this will be the case that there is a widespread hope and expectation that these combined institutions will endeavor to produce investigators as well as practitioners, to give to the world men who cannot only sail by the old charts, but who can make new and better ones for the use of others. This can only be done where the professors and teachers are themselves seeking to increase knowledge, and doing this for the sake of the knowledge itself; and hence it is supposed that from this hospital will issue papers and reports giving accounts of advances in, and of new methods of acquiring knowledge, obtained in its wards and laboratories, and that thus all scientific men and all physicians shall share in the benefits of the work actually done within these walls. But however interesting and valuable this work may be in itself, it is secondary in importance to the future of science and medicine and to the world at large, in comparison with the production of trained investigators, full of enthusiasm, and imbued with the spirit of scientific research, who will spread the influence of such training far and wide. It is to young men thus fitted for the work that we look for the solution of some myriad problems which now confront the biologist and the physician.

Do I seem to ask too much: to be sanguine as to what human thought, and study and skill may accomplish; to forget that there is one event unto all; that the shadow of pain and death come on the wise man as on the fool? I have two answers. As surely as our improved methods of prevention and treatment, based on the advances in knowledge of the last fifty years, have already extended the duration of life in civilized countries nearly five years, have prolonged thousands of useful and productive lives, and have done away with indescribable agonies of the pre-anesthetic period, so surely we are on the verge of still greater advances, especially in the prevention of infectious and contagious disease, in the resources of surgery against deformities and morbid growths, and in the mitigation of suffering due to causes which cannot be wholly removed. But the second answer is more important and it is this: It is our duty to try to increase and diffuse knowledge according to the means and opportunities which we have, and not to rest idle because we cannot certainly foresee that we shall reap where we have strewn. "It is not incumbent on thee to finish the work, but thou must not therefore depart from it," says the Talmud, and "Of him to whom much is given much shall be required," says the Scripture.

These words of Dr. Billings show better than I could express it, the wisdom, the farseeing vision, the ideals and intellectual strength of the man. His influence upon hospital development and medical education cannot be over-estimated. How fortunate that at the very beginning and continuing for many years this institution had the benefit of his influence as a consultant and adviser to the trustees. These words are still full of meaning, and particularly to us officers, teachers and pupils in the institution for which he did so much, and who on this occasion pay tribute to his memory.

DR. JACOBS: The evening would not be complete unless we had Dr. Welch to summarize and to pay his tribute.

DR. WELCH spoke in part as follows: I regard it as one of the greatest influences of my life to have known Dr. Billings. I first became fairly well acquainted with him when I was a student in a pathological laboratory at Leipzig. Dr. Billings came there that winter and stayed several days. He came often to the laboratory, and delightful experiences were the evenings we spent with him in Auerbach's Keller talking about all sorts of things. He had already written about the Johns Hopkins

Hospital and was full of the future of this institution. I saw then one side of his activities—the most characteristic in a way—his extraordinary love of books and knowledge of medical literature.

The central work of Dr. Billings was of course the library of the surgeon-general's office, and the museum, enduring for all time. I question whether America has made any larger contribution to medicine than that made by Dr. Billings in building up and developing the surgeon-general's library and in the publication of the Index Catalogue and the Index Medicus. That in my judgment is our greatest contribution to medicine, and we owe it to this extraordinary man. Enough has perhaps been said as to the qualities of the man who organized and developed that great work. Dr. McCaw has rescued a little chapter in his life about which few knew anything—his experiences as an army surgeon. It is interesting to know how his experiences as an army surgeon influenced his subsequent work. The fact that he was an army surgeon brought him into the surgeon-general's office in Washington; and the opportunity offered there enabled him to develop this great library.

The other work which he did during the thirty odd years of his connection with that library was in a sense incidental to his work as librarian of the surgeon-general's office. Nevertheless this other work was highly significant. He was for a time our leading authority in hygiene in this country, at least in certain important branches. He was actively interested in the work of the American Public Health Association in its early days. I have no doubt that his interest in hygiene came from his experience in the war. In fact, his early publications indicate that; one being on hospitals and barracks; another, on army sanitation which appeared about 1870. Thus, you can trace from his army experience, the work of the library, and also his work in hygiene. The latter of course is not surprising, because an army surgeon should be interested in hygiene and sanitation, as the natural result of his professional interest. Not so, however, his interest in bibliography and the building up of a library, an extraordinary and absolutely unique work for an army surgeon, in a young country like ours. When asked what America had contributed to medicine, you would not expect to reply the building of a library and preparation of an Index Catalogue. You might expect it in a country like France or Great Britain. Nevertheless, that is our contribution, and as Dr. Thayer has said, that library has had a marked influence upon the medical outlook in this country. Greater justice is done here to the discoverer in medicine than elsewhere, and a much more careful effort is made to see that a full record is kept of what has already been done, so that historical justice may be given to previous work; so the very characteristics of our medical literature are in a sense a tribute to Dr. Billings' work.

His work as a hygienist was important. He was the greatest authority on everything relating to sanitation, hospital construction, heating and ventilation. Then he was the greatest vital statistician this country has produced. His connection with the tenth and eleventh census was of the first significance.

The character of the data collected for them was due to the thought which he gave to the matter, and his analysis of the vital statistics of cities in connection with the eleventh census was a most important piece of work. Dr. Billings was the Cartwright lecturer at the College of Physicians and Surgeons in New York in the late '80's and his lectures were devoted to this subject. It is not surprising when he retired from the army, that he should have been selected to be professor of hygiene in the newly founded laboratory of hygiene at the University of Pennsylvania.

Dr. Norton I think is under misapprehension as to his fame. His was our most famous name, so far as European reputation is concerned, with the possible exception of Dr. Weir Mitchell during the decades between 1870-1890. He had the widest acquaintance and was the most highly esteemed of American physicians. He was the one whose presence was desired to represent American medicine on special occasions. He was the recipient of honorary degrees from Dublin, Edinburgh and Oxford. His was a great name and a great influence in the world of medicine.

His influence was also great upon American medicine. I believe he had the making of a great surgeon, but he was withdrawn from active practice. When you consider that he was a librarian, a bibliographer, a writer on hygiene and a writer on sanitation, it is remarkable what his influence was. Of all the men I have ever known, he was about the wisest. He was a man whose judgment you sought on any difficult subject, and you pinned your faith to him more than to any man of your acquaintance. He was wisest because he was under no illusions. He got at the heart and essence of things. He was an eminently sane man, who knew what it was best to do under the circumstances, and what it was practicable to do. This quality was associated with a wide vision and high ideals. Some of his utterances were much resented by the average physician—the somewhat chauvinistic American doctor. Read two of his addresses which made a great stir at the time. One is the centennial address at Philadelphia in 1876 on American medicine. And above all, read the address which was resented by some members of our profession, "Medicine in America," given before the British Medical Association in 1886. Somewhat facetiously, but fairly seriously, he discussed the subject of malaria, and declared that certain portions of this country had been rather sterile in the matter of investigation and prevention. He was half-jocose, but at the same time he candidly stated how meagre had been our contributions. This view was the opposite of the usual Fourth of July, spread-eagle style of address, but it was well to have it said; and he said it well! At the same time I would not convey the impression that he was not a patriotic American. There were none more so, but he put things exactly as they were. He was a lover of truth, and he would spare nothing in order to reach the truth and kernel of a matter.

He was not an educator, but of course his influence on American education was considerable. As has already been pointed out, what this hospital is to-day is mainly the thought of Dr. Billings. He conceived of it as a place not only for the

care of patients, but for teaching and for investigation—the three great functions of a hospital. All three were conceived of as essential parts of its work. He was here as the adviser of the trustees of the hospital from about 1876, I think, or 1877, until the time when the hospital opened. They would have been only too glad to have him become the superintendent of the hospital. It would have been a pity in a sense to have him give up his great work in Washington. Dr. Billings gave several courses of lectures on medical education at the university, and later at the hospital.

The medical school was famous before it existed. There was a great deal of discussion as to what the school was going to be, and no one had more influence than Dr. Billings. There was a little medical faculty here even before I came in 1884. The hospital opened in 1889 and the medical school in 1893, but the records of our medical faculty begin before the opening of the hospital and the medical school. There was a little group, consisting of President Gilman, Ira Remsen, professor of chemistry; Newell Martin, professor of biology, and Dr. Billings, and the data collected by them are extremely interesting. When we planned to open the medical school, our most perplexing matter was the question of requirements for the admission of students—elaborate requirements which represented such a step beyond what existed at that time! Not even a high school requirement generally existed then. We were alarmed at the prospect and had no formal opening of the medical school. We feared that nobody would come, because we felt that we ourselves could not have gotten in and

we did not know whether any such students as we desired existed at that time. Dr. Billings was in our councils, and one of his contributions was a little publication privately circulated, in which he gave the requirements for the doctor's degree in all the leading universities in the world. You may imagine how helpful that was when we were endeavoring to determine our requirements for admission.

Nothing has been said about the great work of his later years as the librarian of the great Public Library in New York. There he supervised the erection of its great building and the consolidation of the three great foundations—the Astor, the Lenox, and the Tilden. He organized the library which in New York they believe to be his greatest work. At the recent memorial meeting in the Public Library—a most interesting meeting—Andrew Carnegie, Dr. Weir Mitchell, Dr. Osler, John L. Cadwallader and others spoke, and emphasis was laid upon it as his greatest and most important work. You can see how great the man was when just at the end I can only touch upon what many believe to be his greatest work. I do not so believe it to be. I think his greatest work was the building up of the library in Washington and the publication of the *Index Medicus* and the *Index Catalogue*. Dr. Osler says the fame of bibliographers lives. Haller will probably be known longer as a bibliographer than as a contributor to knowledge. Gessler will probably be known longest in a similar way. Dr. Billings was the greatest bibliographer in the history of medicine.

DR. JACOBS: These are our tributes to Dr. Billings.

NOTES ON NEW BOOKS.

Meningococcus Meningitis. By HENRY HELMAN, M. D., and SAMUEL FELDSTEIN, M. D. Introduction by HENRY KOPLIK, M. D. Illustrated. \$2.50. (Philadelphia and London: J. B. Lippincott Company, 1913.)

In this monograph of 307 pages, the present knowledge of the meningococcus infections of the meninges is presented. Free use of the clinical material of other workers has been made together with that which the authors themselves have had. The various aspects—bacteriology, epidemiology, symptomatology, etc.—of this disease are considered in a thorough manner. The completed bibliography adds to the value of the work and most of the illustrations are good. The book should prove of usefulness, especially to physicians engaged in clinical work.

Reference Handbook of the Medical Sciences. Edited by THOMAS LATHROP STEDMAN, M. D. Vol. III. Illustrated. Embossed. \$7. (New York: William Wood & Co., 1914.)

With one exception all the contributors to this volume are Americans, the lonely stranger is a Canadian; and the list of names is representative of the best men in the profession throughout the United States. This broad selection of authors gives this handbook authority which would be lacking were it a more local production. It contains a great deal of information not readily found except in a large library, so that it at once becomes a most useful book for almost any physician, if he is willing to wait for all eight volumes. It is a thankless and a most exhaustive task to edit such a work, and one for which few are so well fitted as Dr.

Stedman; he is to be congratulated on getting out these large volumes as rapidly as he does, and in so successfully keeping such a high standard throughout. This handbook can be referred to with the assurance of finding accurate, helpful and reliable information.

Where the lapse of time between the appearance of the volumes is considerable it would seem better to give some definition to every term embodied, and not say "see —," another reference which may not be found until the last volume appears. There are articles in this volume, as for instance, on the "ear," which, it seems to us, could be much shorter. In this article one finds more than in many small works on this subject. One would not naturally turn to such a handbook for information as to how to perform certain operations, so why should these be given in detail? The choice of illustrations might be discussed at length—why some are selected and many others omitted? The reproductions are not remarkable and many are poor. The lists of references appended to papers vary in length and form; there should be more uniformity practiced in their arrangement and abbreviations.

The Unexpurgated Case Against Woman's Suffrage. By SIR ALMROTH E. WRIGHT. \$1. (New York: Paul B. Hoeber, 1913.)

The author has not added to his distinction as a scientific investigator by this work. The fanatic opponents of suffrage have as little reason on their side as the fanatic supporters, and Sir Almroth Wright's plea against giving women the right to vote carries very little conviction and weight with it. The publication of this essay is to be regretted from almost every point of view.

THE QUARTER CENTENNIAL ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL AND THE TWENTY-FIRST ANNIVERSARY OF THE OPENING OF THE MEDICAL SCHOOL

Will be observed by appropriate exercises beginning October 5, 1914, and continuing during the week.

The exercises upon Monday, October 5, 9.30 a. m. to 12 m., are to be especially arranged for by the Training School for Nurses and will be announced later.

Upon Monday at 3.30 p. m., the formal opening meeting will be held at the Lyric, with addresses by Dr. W. H. Welch, Sir William Osler, Miss M. Adelaide Nutting and Dr. H. M. Hurd.

In the evening there will be dinners of the former Medical Officers of the Hospital, and of the Alumnæ of the Training School for Nurses.

Upon Tuesday, October 6, 9.30 a. m. until 12 m., papers upon medicine by former members of the staff will be presented in the Medical Amphitheatre. Papers or demonstrations of methods of study of Psychiatry at the Henry Phipps' Clinic from 10 a. m. to 12 m. Gynecological operations in the Surgical Amphitheatre from 10 a. m. until 1 p. m. A Clinic by Sir William Osler at 12 m.

Luncheon at the Hospital from 1 to 2.30 p. m.

From 2.30 to 3.30 p. m. Clinic in the Harriet Lane Home by Dr. John Howland. At 3.30 p. m., a dedication of the Hewetson Medallion.

A demonstration of Nurses' work in the Medical Amphitheatre from 4 to 5 p. m.

From 4.30 to 5.30 p. m., a lecture on the Herter Foundation by Dr. Thomas Lewis of London.

In the evening a Dinner of the Alumni of the Medical School.

Wednesday, October 7, from 9.30 a. m. to 1 p. m., Surgical Operations in the Surgical Amphitheatre.

From 11 a. m. to 1 p. m. Visits to Medical Laboratories.

1 p. m., Luncheon.

At 3.30 p. m., Dedication of the James Buchanan Brady Urological Clinic, with addresses by Dr. Winford Smith, President Goodnow of The Johns Hopkins University, Dr. H. H. Young, and others.

A Garden Party upon the lawn of the Hospital at 5 p. m.

In the evening a Subscription Dinner to Mr. James Buchanan Brady. Also Class Dinners.

Thursday, October 8, 9.30 a. m. to 1 p. m., Papers in Pathology in the Medical Amphitheatre.

Also Papers or Addresses upon Obstetrical Topics in the Surgical Lecture Room, 10 a. m. to 12 m. Operations in Urological Surgery in the Surgical Amphitheatre, 10 a. m. to 12 m.

1 to 2.30 p. m., Luncheon.

4.30 p. m., Second Herter Lecture by Dr. Lewis.

In the Evening, Class Dinners.

Friday, October 9, 4.30 p. m., Third Herter Lecture by Dr. Lewis.

More detailed programmes will be published later.

During the Anniversary Week laboratory demonstrations will be given in the laboratories of the Medical School as follows:

In the Anatomical Laboratory, By Prof. Mall and the Anatomical Staff.

In the Physiological Laboratory, By Prof. Howell and the Physiological Staff.

In the Pharmacological Laboratory, By Prof. Abell and the Pharmacological Staff.

The exact dates and hours of such demonstrations will be announced in the final program.

PROGRAMME FOR THE CELEBRATION OF THE TWENTY-FIFTH ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL

MONDAY October 5	TUESDAY October 6	WEDNESDAY October 7	THURSDAY October 8
9.30-12 Nurses' Training School	9.30-12 Medicine (Medical Amphitheatre) Psychiatry 10-1 Gynecology (Surgical Amphitheatre) 12 Clinic Sir William Osler	9.30-1 Surgery (Surgical Amphitheatre) 11-1 Medical Laboratories	Pathology (Medical Amphitheatre) Obstetrics (Surgical Lecture Room) 10-12 Urological Surgery (Surgical Amphitheatre)
	1-2.30 Luncheon	Luncheon	Luncheon
3.30 Opening Meeting (The Lyric) Addresses: Dr. W. H. Welch presiding Sir Wm. Osler Dr. H. M. Hurd Miss M. A. Nutting	2.30 Pediatric Wards Dr. Howland 3.30 Dedication Hewetson Medallion 4.30 Herter Lecture	3.30 Dedication of the J. B. Brady Urological Clinic Dr. W. H. Smith presiding Pres. F. J. Goodnow Dr. H. H. Young and other speakers 5 Garden Party (The Lawn)	4.30 Herter Lecture
Dinners Johns Hopkins Hospital Alumni Nurses	Dinner Alumni of Medical School	Dinner to Mr. J. B. Brady, Donor of the new Urological Clinic Class Dinners	Class Dinners

THE HERTER LECTURES FOR 1914.

The Herter Lectures will be given in connection with the Quarter Centennial Anniversary of the Opening of The Johns Hospital and the Twenty-first Anniversary of the Opening of the Medical Department of The Johns Hopkins University, upon Tuesday, Thursday and Friday, October 6, 8 and 9, 1914, at the Physiological Lecture Room, Monument and Washington Streets, at 4.30 p. m., by Thomas Lewis, M. D., University College, London, England.

Dr. Thomas Lewis in charge of the heart station at University College, and Editor of *Heart* has done important work in the study of cardiac conditions, and will present three lectures on the scientific study of the heart and its bearing on clinical medicine. He is the first clinical investigator who has filled the position of Herter Lecturer. The titles of his lectures will be announced later.

BULLETIN

OF

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THE RELATIONS OF INTERNAL MEDICINE TO PSYCHIATRY.*

By LEWELLYS F. BARKER, M. D.,

*Professor of Medicine in the Johns Hopkins University and Physician-in-Chief to the Johns Hopkins Hospital,
Baltimore, Md.*

The subject which I have chosen for my remarks is the relation of internal medicine to psychiatry. Workers in internal medicine who are not psychiatrists will, as a group, look at such a topic from a view-point somewhat different from that of a group of psychiatric workers. Moreover, no two members of either group can be expected to hold identical views, owing to inequalities in innate tendencies and in opportunities for acquiring knowledge. You will not expect me, therefore, with the prejudices of my group and with the bias peculiar to myself, to give expression to opinions wholly satisfactory either to psychiatrists or to other internists. As fellow workers in related fields of natural science, however, your way of looking at mine are sufficiently alike to permit, I hope, of a similarity of view consistent with sympathy and with conditional approval. It is desirable that from time to time various internists and various psychiatrists shall give expression to their views regarding the mutual relations of their respective subjects, for the fruits of such discussion should grow in value with the number sharing in it.

Satisfactorily to deal with my topic, the province of each of the two subjects should be defined; but as with every two sci-

ences which overlap or border on one another, there is likely to be some doubt as to the exact territory of each. As generally understood, *internal medicine* has to deal with the science and art concerned with the restoration and preservation of health by means other than those employed by the surgeon and the obstetrician, while *psychiatry* has to deal with the study and treatment of diseases of the "soul" or "mind," the word "psychiatry" being derived from the Greek *ψυχή*, meaning breath, life, soul, and *ἵατρος*, meaning physician. Thus, out of the larger subject, medicine, dealing with all disease other than that dealt with by surgery and by obstetrics, and including diseases affecting both what has been called the mind (*ψυχή*) and what has been called the body (*σῶμα*), there has developed a special branch known as psychiatry, in which, according to general assumption, special attention is paid to the diseases which affect particularly the mind.

The actual establishment of psychiatry as a subdivision of internal medicine is of comparatively recent development, scarcely more than a hundred years old. In the medicine of antiquity, it is true, disturbances of the "soul" were thought to be associated with bodily disturbances, especially with fever and with changes in the humors of the body, but this medical view of "mental disease" did not obtain during the middle ages. "Mental disturbances" for the scholars and the priests

*Annual Address at the seventieth annual meeting of the American Medico-Psychological Association, Baltimore, Md., May 26-29, 1914.

of that time were not looked upon as evidences of disease but rather as due to demoniacal possession or divine punishment, occasionally to divine ecstasy or rapture. Medical men up to a century ago busied themselves but little with the study and treatment of those who were grossly disturbed "mentally." The treatment these unfortunates received varied with the disturbance. Some of them were lucky enough to be revered and worshiped as saints, but more of them had the misfortune to be regarded as sinners whose only hope lay in a priest who could exorcise evil spirits; all too often, as witches or wizards, practitioners of sorcery, they were made to feel the tortures of the rack or to suffer at the stake.¹ The interest of medical men had become reawakened in mental disease a long time before it became generally recognized that mental disturbances are best studied and treated by physicians, and it was only after the insane began to be treated in a humane manner in hospitals under the care of physicians that the scientific study of "mental disease" could be begun.²

Pinel and Esquirol in France; Reil, Nasse and Jacobi in Germany; Gardner Hill, Tuke and Connelly in Great Britain were the pioneers in ameliorating the conditions by providing medical treatment.³ In America asylums for the insane began to be established in the first quarter of the last century; the propagandism of Miss Dorothea Dix, in the middle of the century, led to great reforms in care, and with the opening of the Utica State Hospital in 1843 began "the era of awakening."⁴ A demand for psychiatric clinics, for the scientific study of "mental diseases," was made by Griesinger in 1868, since when such clinics have been established in Germany in nearly all the university centers. We have begun to follow Germany's example in America; a psychiatric clinic has existed for several years in Ann Arbor; Boston has a psychopathic hospital⁵ which serves a similar purpose, and now Baltimore has the Phipps Psychiatric Clinic. During the past twenty-five years psychiatry, in spite of the obstacles in its way, has developed with surprising rapidity, attaining to general recognition as an important medical specialty. The study of patients by clinical methods has led to the recognition of certain types of abnormal behavior, disorders with characteristic symptoms, course and termination. Psychiatrists, calling to their aid the methods, and utilizing the results, of certain of the more fundamental sciences (anatomy, physiology and embryology of the nervous system, normal psychology, pathological anatomy, experimental pathology, pharmacology, general medicine), have been gradually accumulating data for a foundation upon which a true science of psychiatry may later be built,

a science which will reveal the nature and causes of what are now called "mental disorders" and which will permit man to cure or to prevent them.

When we inquire why it is that psychiatry has been marked off as a special province of internal medicine, to be cultivated for its own sake by a selected group of men known as psychiatrists, rather than by the general practitioners of internal medicine who deal with diseases of the respiratory, circulatory, digestive, urogenital, nervous and other systems of the body, we find the reasons (1) partly in the historical development above referred to, (2) partly in the fact that, for obvious reasons, the markedly disturbed patients with whom psychiatrists first dealt could not be cared for properly except under conditions differing somewhat from those which obtain in people's homes and in the ordinary wards of hospitals, and (3) partly in recognition that abnormal mental states and the pathological behavior which accompanies them require for their investigation a training and an experience both in normal psychology and in psycho-pathology which have, hitherto, not been available to the ordinary graduates of medical schools.

It was, then, chiefly an urgent practical need, that of caring for patients whose extraordinary behavior was such as to preclude medical attention at home and in ordinary hospitals, which led to the development of psychiatry as a special branch of medicine. It is well that this should be emphasized, for as knowledge of psychiatry and of medicine increases, it becomes ever clearer that there is no fundamental difference between the pathological states studied by the psychiatrist and those studied by the general internist. The patients who ultimately fall into the hands of the psychiatrists are usually observed in the earlier periods of their illness for a longer or shorter time by internists, and many patients who remain in the general internist's care throughout the whole of their illness exhibit behavior which would be recognized at once by those skilled in psychiatry as the accompaniment of abnormal mental states.

Some seem to believe that the domain of abnormal "mental states" is identical with that of psychiatry, belonging exclusively to it, while the domain of abnormal "bodily states" is identical with that of internal medicine, belonging exclusively, in turn, to it. Without entering further at present upon what is meant by "mental states" and "bodily states" respectively, it is obvious that to define the provinces of internal medicine and psychiatry in the way mentioned will be satisfactory neither to the psychiatrist nor to the general internist. For a large part of the work of psychiatrists to-day consists in the study of the "bodily states" of their patients *ante mortem* and *post mortem*, and no small part of the work of internists consists in securing from their patients reports of modifications of their "mental states," known ordinarily as the "symptoms" of which the patients complain.

In the study of every patient, an internist begins with listening to a "complaint." If a patient complain of a pain in the abdomen, of a cough, of a feeling of palpitation, of shortness of breath, of diarrhoea, of dimness of vision, of sleeplessness, of disinclination for exertion, of loss of appetite, of numbness

¹ Kraepelin (E.): *Psychiatrie*. V. Aufl., Leipzig, 1896.

² Cf. Ziehen (T.): *Die Entwicklungsstadien der Psychiatrie*. Berl. klin. Wchnschr., 1904, XLI, 777-780.

³ Garrison (F. H.): *An introduction to the history of medicine*. Phila. and Lond., 1913; also, Meyer (A.): *A few trends in modern psychiatry*. Psychol. Bull., 1904, I, 217-240.

⁴ Hurd (H. M.): *Three-Quarters of a Century of Institutional Care of the Insane in the United States*. Am. J. Insan., Jan., 1913.

⁵ Cf. Southard (E. E.): *Contributions from the psychopathic hospital, Boston, Massachusetts: Introductory note*. Bost. M. and S. J., 1913, CLXIX, 109-116.

in his left foot, in each instance he reports a modification of his "consciousness" which has led him to assume that his body is diseased, perhaps, in the part of it which feels abnormal to him. This assumption of the patient may or may not be correct; the internist often finds that the patient's "ideas" of the nature and localization of his "bodily disturbance" are erroneous. The physician uses, however, the psychic (anamnesic) clues as guides to his search for pathological-physiological processes; he hunts for physical, chemical, or biological changes, first in the parts to which the patient has referred him, and also elsewhere in the patient's body; very often he gives but little more thought to the "mind" of the patient who has reported one or several modifications of his consciousness. Now there would seem to be easy transitions from these slighter modifications of "consciousness" which we call the "symptoms" or ordinary "somatic" disease, to the outspoken and complex "mental" syndromes with flagrant maladjustment to surroundings with which the psychiatrist has ordinarily to deal. It is the internist's experience with the pain of gall-stone colic, with the delirium of typhoid fever, with the mental confusion of uræmic intoxications, with the hallucinations which accompany enforced abstinence after alcoholic excess, with the depression which accompanies mucous colitis, with the optimism of the consumptive, with the aphasic, apraxic and agnostic phenomena in cerebral atherosclerosis, with the post-paroxysmal homicidal act of a man who has epilepsy, with the delusions of grandeur in general paresis, with the moral and intellectual defects often seen after disease of the brain in infancy, with the dullness, slow-wittedness and drowsiness of myxœdema, and with the anxiety, apprehension, fear, restlessness and irritability characteristic of exophthalmic goitre, which makes him think of the importance of studying "somatic" alterations when the "mind" or "psyche" is disturbed, and of observing the "behavior" of the patient and of inquiring as to changes in his "mental" states when the "body" or "soma" is obviously diseased.

We might further attempt to express the relation which obtains between internal medicine and psychiatry by applying in pathological domains a modern conception of the relation of physiology to psychology,⁶ and say that internal medicine (exclusive of psychiatry) investigates the processes (under diseased conditions) of the parts, or organs, of which any organism is composed, while psychiatry investigates the activities (in abnormal states) of the organism as a whole, that is, those activities in which it operates as a whole or unit. But from what has been said of the work now actually carried on by psychiatrists on one side and by general internists on the other, it is plain that these definitions are not entirely satisfactory, though they approach the goal and are doubtless akin to the considerations in which psychiatry is defined as "the science which deals with disorders of adaptation or adjustment of the person to the 'situations' in which he finds himself." If we modify this last definition of psychiatry so as to include

only the cases in which there is *conspicuously* abnormal behavior of the person as a whole, we shall come closer to the actual work of the psychiatry of our time. It is not worth while, perhaps, to strive too hard for precision. Even if we could satisfactorily delimit the provinces under discussion to-day, the boundaries would have to be changed a little later on. We must, therefore, forego any attempt at final and rigid mapping, be content with outlining the areas provisionally, and be prepared to change the outlines as the sciences develop, as their methods of study change, or as the needs of practice dictate. Our difficulties would only be increased if we tried sharply to mark out the field of neurology; this doubtless explains why, in some universities, neurology has an independent place, in others is combined with psychiatry, and in still others is kept in the department of internal medicine.

It would certainly not be wise to limit the psychiatrist's studies to what are ordinarily known as the "insanities" or "lunacies," to the patients whose "unsoundness of mind" is, for example, symptomatologically designated as mania, melancholia, dementia, hallucinatory confusion, paranoia, hebephrenia or catatonia, syndromes one or more of which may be met with in the several pathological states known as the manic-depressive psychoses, the idiocies and imbecilities, the toxic and infectious processes, dementia paralytica, the senile dementias, or the psychoses of adolescence (*dementia præcox*). While the practical side of his work may compel him to give the major part of his time to the study and care of such patients, it is mandatory for the advance of his science that he shall have opportunity to study also (1) some of the patients ordinarily described as "nervous" or "psychoneurotic," rather than "insane," I mean, for instance, the "neurasthenic," the "hysterical," the "psychasthenic," or the "hypochondriacal," and (2) some of the patients, presenting the phenomena known as aphasia, agnosia, and apraxia, due to local lesions in the brain. There is no dearth of such material; every community supplies it in amounts adequate to provide for the investigative needs of the psychiatrists, as well as for those of the general internists and the neurologists. It will be all the better if the psychiatrist can add still further to his objects of study and include a certain number of those individuals who are thought not to be actually diseased but only to be psychologically "unusual," for instance, (1) geniuses, (2) those who have undergone or are reported to have undergone peculiar experiences (hypnotic, mystical, psychotherapeutic, telepathic, etc.), and (3) those who manifest so-called anti-social tendencies (*e. g.*, vagrants, prostitutes, criminals).

Indeed, to build up a general psychopathology, whether it have an associational basis, as in the attempt of Ziehen, or a clinical pathological basis, as in the effort of Wernicke,⁷ or be more eclectic, as exemplified by the recent works of Lugaro⁸ and of Jaspers,⁹ a large and varied clinical and pathological

⁷ Wernicke (C.): *Grundriss der Psychiatrie*. 2 Aufl., Leipz., 1906.

⁸ Lugaro (E.): *Modern problems in psychiatry*, Eng. Transl. by D. Orr and R. G. Rows, Manchester, 1909.

⁹ Jaspers (K.): *Allgemeine Psychopathologie*, Berlin, 1913.

⁶ McDougall (W.): *Psychology*, N. Y. (Home Univ. Library), 1913.

experience is desirable. The general psycho-pathologist can, however, in his constructions, make good use of the results of intensive studies made in more circumscribed fields. He must know how to value in the first place researches dealing with the subjective phenomena of mental disease (phenomenology), whether these are reported by patients as referring to external objects, to persons other than themselves, or to their own bodies, and including not only cognitive states but also feelings and emotions (affective states), and consciousness of effort or striving (conative states). He must understand also how to estimate the objective symptoms of "mental disease," the objectively demonstrable disturbances of perception, comprehension, orientation, association, memory, motility, speech, the bodily expressions of mental states (physiognomy, writing, work, behavior). He will pay attention especially to reports of investigations undertaken from the experimental side.¹⁰ Besides utilizing these studies bearing upon the subjective and objective elements, he has further to determine the worth of researches which deal with the connections which exist among the subjective phenomena, that is, with the way in which systems and dispositions develop in the mind in disease and with the manifestations of the abnormal "structure of the mind" in the so-called "pathological reactions,"¹¹ in "pathological suggestibility," in "pathological after-effects of earlier experiences," or in the splitting off of smaller or larger systems and dispositions from the mind as a whole ("dissociation of personality"). In this domain come also the observations upon the attitude of the patient toward his own disease, whether it be one of total "perplexity," or one in which he more or less critically observes his own mental state and decides that it is either normal or abnormal (absence or presence of so-called "disease-insight").

The worth of investigations of the connections existing among the elements on the objective side has also to be weighed and judged by the all-round psychopathologist. These connections appeal especially to the worker who has been trained in biology, physics and chemistry, for it is in them that he believes that causal explanations are to be sought. Regarding the structure and functions of a living organism as the resultant of the interactions between factors of heredity and factors of environment, he will enter upon the Herculean task of analyzing, in an individual case, the reciprocal influences of exogenous forces and the innate tendencies derived from the patient's progenitors. Here all the methods of internal medicine—physical, chemical and biological—have to be employed. It is only on a basis of studies such as I have referred to that we can hope in the future for a satisfactory general psychopathology, one adequate for application to the clinical syndromes which we meet every day either as psychiatrists or as general internists. And as our knowledge of general psychopathology grows, our classification of the psychoses and

psychoneuroses will gradually change. Clinical syndromes will be multiplied or reduced as further knowledge permits of greater discrimination on the one hand or of better syntheses on the other. Psychological classifications will arise on the subjective side, while on the objective side pathological-histological, chemical, physical, and biological classifications will be established; and, most important of all, we shall ultimately arrive at the groupings which are so important for prevention, namely the etiological.

I have spoken of "consciousness"¹² as though there were no doubt that it occurs. But we live in iconoclastic times, and there are people who deny the existence of "consciousness" as they do that of "ideas" and the possibility of "introspection."¹³ Now medical men, as a rule, have had but little training in psychology or in psychophysics. They have had an education in natural science (physics, chemistry and biology), and in the laboratory and clinical branches of medical science. They take it for granted that they are conscious organisms themselves, that other human beings and perhaps animals are conscious, and that consciousness is experienced by lower animals, by plants, or by inanimate objects in the external world must be very unlike their own. They are familiar with different grades of consciousness in themselves from the full awareness of alert states through the lessened awareness of dreams to the "unconsciousness" of deep sleep or of ether-anæsthesia. This consciousness occurs in the same living body which they study in other ways:¹⁴ they do not think of it as anything separable from the living body; it disappears sometimes while the body is alive; they think that human and animal consciousness ceases to exist, as such, at death and often at a considerable period before death when this is preceded by coma.¹⁵ Familiar with the conceptions of development and of adaptation, they think of the gradual evolution of consciousness in each human individual as well as in the animal series; they think of it as having its origin in lower forms of mentality, for they do not think of attributing to the amœba any awareness comparable to their own; since, however, they see a graded series of living organisms extending all the way from the protozoa to man, it is not hard for them to think of similar gradations in the "mental" or "psychic" all the way up to the "mind" of man from the "protoæsthesia" of the amœba. Indeed some medical men, as did Paracelsus and Jerome Cardan centuries ago, can go further and conceive of a "psychic" side to the inorganic world (as in the doctrines of hylozoism and panpsychism).¹⁶ On account of their training in biology and in evolution, physicians think of the mind as developing

¹² Cf. Marshall (H. R.): *Consciousness*. N. Y., 1909, 1-685.

¹³ See the interesting discussion of this subject by Lovejoy (A. O.), *On the existence of ideas*. Johns Hopkins Univ. Circ., n. s., 1914, 178-235.

¹⁴ Kraus (F.): *Die Abhängigkeitsbeziehungen zwischen Seele und Körper in Fragen der inneren Medizin*. *Ergebn. d. inn. Med. u. Kinderheilk.*, Berl., 1908, I, 1-46.

¹⁵ I am, of course, not referring here, in any sense, to the ultimate problem of the "immortality of the soul."

¹⁶ See articles on these subjects in Eisler (R.), *Wörterbuch der philosophischen Begriffe*. 2 Aufl., Berlin, 1904.

¹⁰ Cf. Hoch (A.): A review of psychological and physiological experiments done in connection with the study of mental diseases. *Psychol. Bull.*, 1904, I, 241-257.

¹¹ Meyer (A.): The problems of mental reaction-types, mental causes, and diseases. *Psychol. Bull.*, 1908, V, 245-261.

parallel with the increasing complexity of the mechanisms of regulation and association, that is, with the advancing intricacy of the nervous system, in organisms struggling for their own existence and that of their species. They find it natural, therefore, to look upon "consciousness" and upon "infraconscious mind" as in some way indissolubly connected, in human beings and in the higher animals, with the physiological processes going on in the nervous system and the sense organs. They are sympathetic with the doctrine of various levels of reflexes in the nervous system; they recognize that the activities of the lower levels may not be associated with consciousness but think it possible, with Knight Dunlap,¹⁷ that no consciousness occurs without complete arc-reflexes involving the higher levels. In examining the writings of workers in psychology, physicians sometimes find it difficult to understand all that is said in the discussions regarding (1) the difference between "consciousness" and its "content" and (2) the subject-object relationship! Medical men are, however, conscious of "knowing" and "feeling" and "striving" themselves, and they note that these processes occur in cycles which tend naturally to end in feelings of "satisfaction." Observing other people's behavior, they conclude that these others also "know" and "feel" and "strive." They realize that they can be conscious not only of content which is "present" (intuition) but also of content "not present" (imagination). They can recall the past (recollection); learning, too, that what they are conscious of at any given moment has its "meaning" because of earlier experiences, they speak of "memory" and try to explain it by conceiving of some structural modification of the nervous system that endures, labelling the record a "mental disposition" or an "engram." They see that, as minds develop, these "mental dispositions" become exceedingly numerous and are systematically arranged in smaller groups, larger groups and finally in one vast system; on the cognitive side, the total accumulation constitutes, abstractly considered, the "knowledge" possessed by the mind, while on the affective and conative side the total accumulation, abstractly considered, constitutes the "character" of the individual.¹⁸

Especially interesting to physicians and psychiatrists are the systems of mental dispositions which pertain to the body of the individual in contrast with those which pertain to the "world" external to that body. In all conscious states the background is formed by somatopsychic constituents, that is, by elements referable to the body itself, including the kinæsthetic and visceral sensations, the innervation-feelings, the appetites, and the aversions, and the various so-called affective or emotional states. Our bodies are always "with us"; they are being continually experienced in our conscious states; the "content" corresponding to these bodies is relatively constant as compared with the infinite variation of the "content" corresponding to the external world. No wonder that this "content" pertaining to the body seems to be peculiarly our own;

it is "private" content in contrast with that content which (in a sense, but only in a sense) can be publicly shared. No wonder that we speak therefore of the "self," and define introspection in the narrower sense as "observation of the self," remembering, however, that in the wider sense introspection may refer to examination of the total content. Nor is it surprising that many find it desirable to designate the "observer" as the "I" or "Ego," the "subjective correlator of experience" in contrast with "what is observed," *i. e.*, with the content ("self" and "not self").¹⁹ In this connection it is well to keep in mind the fact that the body is an agglomerate of organs and that the conditions dealt with by the physician often involve gross alterations in the elements of this organ-agglomerate. It is surely not surprising, that somatic disease is often accompanied by alterations in the "self" which have a peculiar tendency to persist and to be characterized by negative feeling tones.

Medical men are not likely to give up the study of consciousness or to refuse to use the reports given by patients of their "subjective" experiences.²⁰ Such a policy would seem to them absurd. But wedded as they are to the method of investigation of the natural sciences, they welcome objective methods of study whenever these are feasible. This predilection, together with the naturalist's tendency to resort when possible to comparative²¹ and genetic methods, accounts for the physicians' sympathy with the "behavior psychology" of our time. The study of animal behavior by men like Loeb²² and Jennings²³ has given us entirely new conceptions of instinct and of intelligence, of the nature of so-called "purposive activities," of the bases of human nature, and of the evolution of mind in the animal series up to man. Recently a number of psychologists—the so-called behaviorists—have tried to eliminate introspective methods in psychology and to describe the whole mental life of man in terms of "expression" or "behavior." Starting with the conception of the neuropsychic reflexes (inherited nervous mechanisms modified by past individual experience) they study the responses to external stimuli (reflex responses) and to internal stimuli (automatic responses) as manifest in movements, vasomotor activity, or gland secretion. In this country, Watson²⁴ and Meyer²⁵ are well-known advocates of behavioristic studies. Recently the Russian neurologist, v. Bechterew,²⁶ in a book entitled "Objective Psy-

¹⁹ Cf. Dunlap (K.): *loc. cit.*

²⁰ Cf. Angell (J. R.): *Psychol. Rev.*, 1913, XX, 255-270.

²¹ Cf. Herrick (C. J.): Some reflections on the origin and significance of the cerebral cortex. *J. Animal Behavior*, 1913, III, 236.

²² Loeb (J.): *Comparative physiology of the brain and comparative psychology*, N. Y., 1900, 1-309; also, *The mechanistic conception of life*, Chicago, 1912, 1-232.

²³ Jennings (H.): *Behavior of the lower organisms*. N. Y., 1906, Macmillan Co., 380 pp., 8°.

²⁴ Watson (J. B.): *Psychology as the behaviorist views it*. *Psychol. Rev.*, 1913, XX, 158-177; also, *Image and affection in behavior*. *J. Phil., Psychol., etc.*, 1913, X, 421-428.

²⁵ Meyer (M.): *Fundamental laws of human behavior*. 1911.

²⁶ v. Bechterew (W.): *Objective Psychologie*. Leipz. and Berl., 1913, 1-468. See Review by H. C. Warren in *Science*, N. Y., 1914, n. s., XXXIX, 426-428.

¹⁷ Dunlap (K.): *A system of psychology*, N. Y., 1912; also, *Images and ideas*. *J. H. Univ. Circ.*, 1914, 161-177.

¹⁸ Cf. McDougall (W.): *loc. cit.*

chology" has made a consistent and fairly successful attempt to view human psychology from this standpoint. The "conditional reflexes" (involving associative memory) can be studied in several ways. Pawlow taught us the use of the "salivary method" in the dog; Weber, in Kraus's clinic in Berlin, worked with the vasomotor method; Bechterew uses a special method, that of motor association reflexes. In studying the more specialized forms of complex responses, Bechterew describes the "concentration-reflex" (the behavior analogue of attention), the "symbolic reflex" (analogue of language), and the "personal reflex." As a program of study likely to be fruitful, behavior psychology would seem to be highly commendable; but in its more dogmatic statements, its denial of the value of introspective methods, its total repudiation of "images," medical men are not likely wholly to concur.

Internal medicine and psychiatry, confronted as they both are by the problems of the physical and the mental,²⁷ must obviously be directly and deeply concerned with the nature and origin of knowledge (epistemology) and with the nature of reality (ontology). Starting out, as every one must, with naive notions regarding the world of things we know and as to how we know it, physicians come gradually and more or less unconsciously to the adoption of certain epistemological and ontological theories. Though there is no unanimity in opinion among medical men, their special training and experience make them much more sympathetic with some tendencies than with others. First of all, they desire to stick close to experience, lauding the empirical and deprecating the speculative; but, despite this tendency, which on the whole is a good one, they often refuse to theorize when it would be helpful, and they are ever unconsciously transcending experience. In the second place, brought up in the school of the natural sciences, saturated with mechanistic explanations, the medical mind has a structure which predisposes it, at least at the beginning of its critical and philosophic interests, to what metaphysicists designate as materialism and realism, rather than to what they call idealism.

On talking with a number of the more reflective among the medical men I know, and on reading opinions in the literature, it would seem that the critical medical mind of to-day is appealed to especially by the natural-science theory of knowledge²⁸ (W. K. Clifford, Karl Pearson, E. Mach, W. Ostwald, H. Poincaré), but as regards theories of being it is less uniformly responsive. Many physicians lean toward a phenomenal idealism which is not far removed from realism (*e. g.*, Immanent Philosophy of W. Schuppe; Empirio-criticism of Avenarius; Energetics of W. Ostwald and Lasswitz); others adopt a personal idealism (*e. g.*, Humanism of Schiller; Pragmatism of W. James, J. Dewey, and H. Bergson); still others are captivated by some form of realism (*e. g.*, Intuitive Realism of the Scotch School; Synthetic Philosophy of H. Spencer; the New

Realism of Woodbridge, Montague, Holt and S. Alexander). Occasionally a physician adopts an out and out idealism (*e. g.*, Neo-Hegelian Rationalism or Absolutism of B. Bosanquet; of J. Royce), and, here and there, one, reflecting upon the issues between the realists and the idealists, accepts a kind of synthesis of pragmatism and rationalism, trying to avoid the extremes of each (*e. g.*, Theism of J. Ward; of E. H. Griffin²⁹). A large number of medical men decline to let their *pia mater* be stretched by metaphysical considerations at all; many assume either an agnostic attitude, or at least one of suspended judgment.³⁰ Psychiatry, then, as I see it, is a large and very important chapter of Inner Medicine. Every internist should have at least some training in psychiatry, and every psychiatrist should be well-versed in the fundamental facts and methods of study of general medicine. Psychology—both introspective and behavioristic—is just as important as a preliminary study for the prospective medical student as physics, chemistry and biology.

Considering the disadvantages under which psychiatry has worked in the past, the science is certainly to be congratulated upon the fine minds it has attracted and upon the results it has accomplished under difficulties. Full of fascinating problems, psychiatry is in the near future, I venture to aver, likely to prove a formidable rival of all the other medical specialties for the affections of the better young men now entering upon medical careers. We have only to think of the very important social relations of psychiatry to understand that this must be so.

Contemporary psychiatry shows no timidity in the tasks it is assigning itself.³¹ On the contrary, it manifests an ardor and a courage typical of youth. It does not limit itself to the mere study of the insane or the manifestations of insanity. It desires to investigate the cerebral events underlying the abnormal mental states. It is not satisfied with normal psychology or with brain-anatomy and brain-physiology as they exist to-day, and insists, that at least some psychiatrists make contributions in these fields. It studies the pathological anatomy and histology of the brains of the mentally diseased, but it does not stop at the local changes in the brain; it studies also the changes in other organs of the body, seeking abnormal processes there which can account for abnormal brain processes. Then it tries to discover in a faulty heredity, or in environmental influences, explanations of these abnormal processes. Psychiatry studies also the evolution of mind in the individual and in the animal series, and tries to relate this evolution to studies in comparative anatomy and physiology. It does not try to escape from the borderlands of philosophy and metaphysics, but actually ventures into these neighboring territories, taking part, as we have seen, in attempts to construct a theory of knowledge and theories as to the nature of reality.

²⁷ Cf. Warren (H. C.): The mental and the physical. Psychol. Rev., 1914, XXI, 79-100.

²⁸ For a good epitome of such views, see Kleinpeter (H.): Die Erkenntnistheorie der Naturforschung der Gegenwart. Leipz., 1905, 1-156.

²⁹ Cf. Griffin (E. H.): Some present-day problems of philosophy. Johns Hopkins Univ. Circ., 1914, 140-160.

³⁰ For welcome summaries of current philosophical views, see (1) Perry: Present philosophical tendencies . . . , and, Caldwell (W.): Pragmatism and idealism. Lond., 1913, 1-265.

³¹ Cf. Lugaro (E.): *loc. cit.*

Psychiatry has, surely, no narrow conception of its plan of work.³² The technical knowledge demanded for a successful attack upon all its problems is enormous. The methods of a whole series of subsidiary sciences must be drawn upon. No single investigator, of course, can hope to be active in all parts of this large and varied field of inquiry. Not even the collective activities of the members of a single psychiatric clinic can cultivate more than a small portion of the field. The work is cut out for the aggregate of the world's psychiatrists for at least many generations ahead.

The general internist can, perhaps, do most to help psychiatry progress by studying carefully the bodily "equivalents" of psychic phenomena, the contractions of striped and

³² Cf. Meyer (A.): A short sketch of the problems of psychiatry. *Am. J. Insan.*, 1897, LIII, 538-549.

unstriped muscles, the activities of the glands of external and internal secretion, the respiratory and vasomotor changes, and the modifications of cœnæsthesia. Present-day studies of the abnormalities of the functions of the autonomic nervous system³³ on the one hand, and of the diseases of the ductless glands (endocrinopathies)³⁴ on the other, and their relations to the mind, are instances which illustrate the possible influence of Inner Medicine on a developing Psychiatry. We have far to go, but we are on the way.

³³ Cf. Barker (L. F.) and Sladen (F. J.): The clinical analysis of some disturbances of the autonomic nervous system, etc. *Trans. Asso. Am. Phys.*, 1912, XXVII, 471-502; also, Barker (L. F.), the clinical significance of the autonomic nerves supplying the viscera, and their relations to the glands of internal secretion. *Can. Med. Asso. J.*, Montreal, Aug., 1913.

³⁴ Biedl (A.): *Innere Sekretion*. II Aufl., Wien, 1913.

KORSAKOW'S PSYCHOSIS OCCURRING DURING PREGNANCY.*

By DAVID K. HENDERSON, M. D.,

Resident Psychiatrist, The Henry Phipps Psychiatric Clinic, The Johns Hopkins Hospital.

During gestation or the puerperium various forms of paralysis may occur, which may be either of (1) central or (2) peripheral origin. For instance, many cases of hemiplegia have been described which have developed during childbirth either as a result of a hæmorrhage, embolus, or thrombus, and it is by no means rare to meet with cases of paralysis of the peripheral nerves either of traumatic (*e. g.*, from pressure on the nerves as they pass through the pelvis), or of toxic origin. It is this last form—the so-called toxic form—to which I want to direct attention. The earliest reference to this subject which I have been able to find is an article written in 1854 by Fleetwood Churchill "On Paralysis Occurring During Gestation and in Childbirth." In this article Scanzoni of Wurzburg is quoted as having said that paralysis of the lower extremities may in some cases be due to pressure, but in other cases, as the paralysis did not appear until some time after labor, and as a similar affection is known to have attacked the upper extremities, pressure could not be the sole cause, *and it may be attributed to some more profound derangement*. Furthermore, Churchill described as occurring with pregnancy a series of 35 cases of various forms of paralysis, 22 of which occurred during pregnancy, and 13 either during or a short time following delivery. Unfortunately the case records are exceedingly brief, and the cases in the light of our present-day knowledge are so indefinite and heterogeneous that it becomes difficult to estimate even approximately how many of these cases were really cases of peripheral neuritis due to an unknown toxin, how many were of central origin, and how many were of psychogenic origin. To my mind there is no doubt but that some of these were cases of polyneuritis, due to the process of gestation, but owing to the somewhat

imperfect description one would hesitate to make use of them. In 1867, however, Boulton described the case of a multipara, 38 years, who during the eighth month of her pregnancy lost the use of her limbs; could not stand; could not grasp anything, but was able to move her extremities fairly well. Her sensibility was also much diminished. Later her knees became contracted, and pain was experienced in extending them. She was constipated, her appetite was poor, and she fell off in weight. In regard to her mental condition, it is stated that she answered questions rationally, *but her memory was entirely gone*.

Two months after coming under observation she was delivered of an eighth month child in a state of decomposition. The patient made a good recovery from her confinement, but did not improve in memory, for in less than one week she had quite forgotten that she had ever been confined. The above case is no doubt one of polyneuritis, occurring during pregnancy, but except for a few other isolated case records the subject appears to have received scant attention until Möbius, in 1887, put together a series of seven cases of peripheral neuritis, affecting principally the median and ulnar nerves. Möbius' cases all showed themselves during the puerperium, but he advanced the hypothesis that they were probably due to some form of poison formed during gestation. In addition to those forms of neuritis localized to one limb, Möbius in a further communication in 1890 described a generalized form in a woman 30 years old, who four weeks after confinement complained of pain in the left hand, and pricking and burning sensations in both hands. Later the strength of her arms and legs became considerably diminished; all the muscles were flaccid, and wasting occurred in the hand muscles. Möbius makes no special mention of the mental condition in any of his patients. It is not until the appearance, in 1887, of Korsakow's classical de-

* Read in abstract before the American Medico-Psychological Association, May 28, 1914.

scription of the polyneuritic syndrome that we begin to have a more thorough understanding of the disease.

Korsakow grouped together a number of cases of apparent toxic origin, associated with polyneuritis, which were characterized by poor power of retention for recent events, disorientation for time and place, misidentifications, and confabulations, *e. g.*, the description of fictitious journeys and episodes. It was found that this psychosis developed most frequently on the basis of chronic alcoholism, but that it also occurred in connection with other toxic, and infective agents, *e. g.*, in febrile states, lead poisoning, and pregnancy. *Later investigation also showed that the polyneuritic symptoms need not be a constant accompaniment of the psychosis.*

Korsakow reported the case of a woman, 28 years, who towards the end of gestation had œdema of the legs, as well as pain in the limbs, and in the neighborhood of both sciatic nerves. On October 3, 1880, a dead, decomposed child was born. On the next day the patient was in an excited, confused, fearful state. Later she developed anæsthesias and paræsthesias of her extremities, the muscles of the lower limbs were paralyzed, and then the extensor and interossei muscles of the arms and hands became affected, and finally the back and abdominal muscles. Pain was present in the back, in the arms, and in the region of the fifth nerve. Choreic and athetoid movements developed in the legs and arms, and there were also present twitching of the face muscles, swallowing difficulty, and a transitory speech disturbance. It was exceedingly difficult for the patient to concentrate her attention, her memory was poor for recent events, particularly for time, so that she could not tell whether an event had happened the day previously or three years previously. She asked the same question over and over again. After a period of ten months a marked improvement had taken place in the patient's condition. After a period of four years the patellar reflexes returned.

Owing to the fact that cases of Korsakow's psychosis occurring during gestation are exceedingly rare, I have felt that it would be of considerable interest to report two further cases, one of which was associated with a tremendously generalized polyneuritis, while the other showed no polyneuritic symptoms, but mentally the picture was characteristic.

CASE 1.—A young married woman, 31 years, was admitted to the Henry Phipps Psychiatric Clinic on September 4, 1913. She had come of a healthy stock, and had developed normally. She married in April, 1906, and in April, 1907, her first child was born. During this first pregnancy she suffered from nausea and vomiting for three or four months, but did not show any nervous manifestations. The delivery was instrumental, but the puerperium was normal, and she nursed the child for nearly one year. Up until the onset of the present trouble she had been in her normal good health. Early in May, 1913, the patient became pregnant for the second time; towards the end of the same month her appetite became poor, and she started to suffer from nausea. During the months of June and July she was vomiting almost constantly, and lost from 30 to 40 lbs. in weight. She became terribly weak, could only walk with assistance, and it was noticed that her feet would flop. In July, 1913, numbness in feet, legs, and hands developed, but up until

about August 6, 1913, she was able to take a step or two. No mental disorder of any kind was noticed until about August 2, 1913, when one morning she suddenly made a number of entirely false statements, *e. g.*, that she had had three glasses of milk (when she had only had one), that a certain young lady had been to see her, that her sister had brought a red-haired girl into the room, that her brother (dead for four years) was downstairs, and when asked to go to town said that she had been there already that morning and was too tired to go again. She became depressed and tearful, thought that her husband was sick, and would cry in a hysterical way on seeing him. She did not seem to have any realization of where she was, kept absolutely no track of time, and when her birthday came around on August 4, denied that it was her birthday. On account of the fact that the patient, both mentally and physically, was getting rapidly weaker it was determined, on August 9, to produce an abortion, the patient now being three months pregnant. A slight laceration of the cervix resulted, her temperature became very slightly elevated, but the blood and urine examinations were negative, except for a somewhat diminished urea output, which a few days later became normal. Almost immediately after the abortion she became delirious, was fearful, thought that she was on a ship, that the ship was sinking, that some one was after her father to kill him, that the house was on fire, and that the fire was coming into her room. She then seemed to lose her voice, could only talk in a whisper, and had great difficulty in breathing. About ten days after the abortion had been performed she lost power in her hands completely, had incontinence of urine and feces, and became very dull. The patient had never at any time been addicted to the use of alcohol, and there was no known source of infection to account for her sickness.

On admission (September 4, 1913), the patient was delirious, and showed a very unstable emotional condition, laughing one minute and crying the next. She seemed frightened, talked constantly of having been bitten by a dog, but could not tell when, and frequently answered questions in an irrelevant way. She thought that the dog was in the room with her (visual hallucination), and said that she wanted to go and see the doctor about the dog-bite. She misidentified the physician and the nurse, and stated (erroneously) that another gentleman present was the physician's brother. She was completely disoriented for time and place, said that the month was February (September), could not tell the day or the year, and thought that she was still in her home town. She had no realization of her condition, denied that she had any trouble in any way, but admitted that her head felt dizzy.

Physically.—She was in a weak, exhausted, poorly nourished condition, and showed the characteristic symptoms of a generalized polyneuritis; *e. g.*, her hands were flexed at the wrists, extended at the metacarpal-phalangeal joints and flexed at the phalangeal joints (double *main-en-griffe*). She had a symmetrical atrophy of the small muscles of the hands on both sides, and except for occasional slight separation movements, could not move the fingers. The muscles of the forearms were also symmetrically atrophied and flabby, and she could not extend her wrists or carry out pronation and supination movements of the forearms. The muscles of the upper arms were fairly well preserved, so that she could raise her arms above her head. Her feet were kept extended in the position of talipes-equinus, and she was quite unable to move either her toes or her ankles. The muscles of the calves were atrophied and flabby, but at the knee and hip joints she could carry out weak flexion and extension movements, and could abduct and adduct the legs. She could not grip at all with either hand, and could not stand or walk. Her sensory functions were exceedingly difficult to accurately test, owing to her ready exhaustion, and to her confused mental condition. A rough examination showed that to touch sensa-

tions over the hands and forearms on both sides there was a sluggish response, and at times she failed to reply at all when touched on the hands or fingers. She failed to respond to pin-pricks over the hands and fingers, and could not differentiate between the head and point of the pin. This anæsthesia and analgesia gradually lessened up to the elbow on either side; above the elbow the sensibility to touch and pin-pricks seemed about normal. Thermal sensations were more or less accurately differentiated all over.

In the legs and feet the sensory disturbances were analogous to those obtained in the upper limbs; there was an anæsthesia and analgesia extending and gradually decreasing up to the knee-joint. Above the knee there did not seem to be any definite sensory disorder. Marked tenderness was elicited on deep pressure of the muscles of the legs and arms. The tendon and superficial reflexes were completely abolished on the two sides; there was involuntary micturition and defæcation.

With faradic stimulation so much pain was elicited that the examination could not be thoroughly carried out. To galvanism the dorsal interosseous muscles of the feet gave a typical reaction of degeneration, the anodal closing contraction being greater than the cathodal closing contraction; otherwise over the hands and forearms, and legs, the response to galvanism was sluggish, required a large current and the anodal closing contraction approximated the cathodal closing contraction.

In addition to the above, she had a double adductor paralysis of her vocal cords (Dr. Slack), in consequence of which she could not speak above a whisper. She showed a well-marked tachycardia, her pulse rate varying from 130 to 140 per minute, and being irregular in rhythm. Her breathing was entirely costal, owing to the fact that her diaphragm seemed completely paralyzed, and during inspiration the abdomen instead of being protruded was retracted; her breath rate varied from 32 to 40 per minute. There was no disease of the internal organs, and no difficulty in swallowing. Her temperature was 99.8°. A pelvic examination by Dr. Guy L. Hunner, blood examinations, and cultures from the throat were entirely negative. There was a trace of albumen in the urine.

Following Admission.—For several days the patient continued to show a very unstable, emotional condition; at one time she would be bright and laughing, and then again restless and tearful. At nights especially she would get fearful, would think that she was going to be killed, and talked a great deal about people dying. She suffered from visual hallucinations, insisted that people were hiding behind her bed, that some one was trying to kill her child, that bed-bugs, which she attempted to kill, were crawling over her. She remained completely disoriented for time and place.

On September 12, 1913, she was noted as much stronger; her temperature was 99.5°, her breathing was still entirely costal in type, varying in rate from 28 to 32 per minute, her pulse rate was still from 130 to 140 per minute, but was of much better force and volume than previously. She stated that she felt much less fearful than formerly, and only suffered from occasional visual hallucinations at night. Her head felt confused, she continued to misidentify those around her, and confabulated, saying that yesterday she had been up, had gone out driving, and paid a visit. She was still completely disoriented for time and place. Her power of retention was found to be exceedingly poor, as after two minutes she had entirely forgotten an address, the name of a city, and a color, which she had been asked to remember; even after three readings she was quite unable to give the gist of any short story read to her.

On the morning of September 18, 1913, it was noticed that the patient was in a semi-stuporous state, and during the day had a spell of tremendous excitement, waved her arms about, had an agonized expression, and complained of a sensation of smothering.

Her pulse became weak and irregular, so that it could hardly be counted, her breathing was quick, intense, about 36 per minute, and her temperature rose to 102 degrees. For three days her condition was exceedingly critical, and she had to be frequently stimulated with strychnine, digitalis and camphorated oil. She finally made a remarkable recovery, and on October 1, 1913, she was able to speak more clearly, but her voice was still husky. She now seemed to have a better realization of things in general, but she still continued to be confused, was exceedingly emotional, and still remained disoriented for time and place. During October she showed a gradual and marked improvement both mentally and physically. She now did not confabulate at all, did not suffer from any hallucinations, and became oriented for place. She continued, however, to be very emotional, laughed and cried in an impulsive way, and was quite unable to keep track of time. Perhaps the most striking thing in her condition now was the marked defect in her power of retention; she would ask the same questions over and over again and in a few minutes after being visited by her friends had no recollection of their visits.

Physically, her voice was now quite natural, but in speaking she would hesitate and stutter over difficult words; her respiration was still costal in type, but was slower and easier, and now varied in rate from 24 to 28 per minute; her pulse continued to be on an average 130 per minute, but her temperature was quite normal. She regained control over her bladder and bowels. Her arms and legs became much less tender, and she became able to carry out slight movements in the fingers, wrists and ankles. Menstruation restarted, and has been quite regular ever since. Since November, 1913, the patient has gone on steadily improving in every way. At the present time (April, 1914) she is bright and interested in everything that goes on around her. Her general behavior is that of a normal person, but as tested by word-pairs, short stories, repetition of numerals, and so on, her power of retention is still poor, but has considerably improved. Her memory for remote events is excellent. Emotionally, she is rather unstable, but gradually is getting better and better control of herself. Physically, she is able to take part in the occupation classes, can embroider, and can attend to herself generally. She can take a few steps without assistance, and can walk from 20 to 30 yards with assistance. Her cutaneous sensory disorders are improving, there is no tenderness elicited on deep pressure of the muscles, but the tendon reflexes cannot be elicited. Her pulse rate varies from 90 to 108 per minute, and her breathing is now thoracico-abdominal in type. Arrangements have been made for the patient to leave the hospital in a few weeks.

The case may then be briefly summarized as follows:

A multipara, 31 years, in the first month of her second pregnancy started to suffer from nausea and vomiting, and rapidly lost in weight. She then complained of numbness and weakness in the feet, legs, and hands. She became depressed, started to fabricate, lost track of time, and was getting worse so rapidly that an abortion was performed when the patient was three months pregnant. A delirium with fear reaction ensued, she lost power in her hands completely, had incontinence of urine and feces, aphonia, paralysis of the diaphragm, and, probably, also at this time, tachycardia.

On admission to the hospital the patient was delirious, and showed the characteristic symptoms of a generalized polyneuritis. In addition, she had a double adductor paralysis of the vocal cords, and involvement of both the phrenic and vagus nerves. During her hospital residence the striking points in her mental condition have been the exceedingly poor power of retention, the tendency to confabulate, and the un-

stable emotional condition. Both mentally and physically a wonderful improvement has resulted.

The second case which I wish to report is, also, exceedingly interesting, and differs from the first in that the psychosis was not accompanied by any polyneuritic symptoms.

CASE 2.—F. I., 37 years old, was admitted to the Henry Phipps Psychiatric Clinic on December 21, 1913.

Family History.—Paternal grandfather was excitable, and her paternal grandmother had hysterical spells. Her maternal grandfather was eccentric. Her father, one brother and two sisters were described as nervous.

Personal History.—The patient was the youngest of a family of seven. She is stated to have been a healthy child, and to have developed normally. She was clever at school, and was interested in everything. She was very even-tempered, was not extreme about anything, and was devoted to her family and home. In 1896 she married, when 20 years old; her married life was exceedingly happy. Except for an attack of typhoid fever one year after marriage she had been perfectly well up until the onset of the present sickness. She had never taken any alcohol, and no history could be obtained of any toxic or infective agent. She had had three previous pregnancies, each of which had been accompanied for two months by vomiting, but in none of these pregnancies were any nervous or mental symptoms noticed.

Onset of Present Sickness.—The patient became pregnant for the fourth time about August, 1912. During the second month of her pregnancy she started to suffer from uncontrollable vomiting, which continued during her entire pregnancy. On account of her vomiting she was nourished during the last five months of her pregnancy principally by nutrient enemata, and altogether lost from 60 to 70 pounds in weight. Her labor was easy, and a full term healthy child was born on March 24, 1913. For two months previous to the birth of her child her husband had noticed that she could not remember things that happened from day to day, but remote events were accurately retained. She described herself as confused, complained of a feeling of pressure and weight in her head, but knew every one around her and was clear in regard to her surroundings. She became apathetic and uninterested, and after the birth of the child hardly seemed to realize that she had had one. About two months after the birth of the child she accused her husband of infidelity; stated that something had been put into a glass of water to affect her, and later that her mind was full of all kinds of profane thoughts. She tended to fabricate, said that a physician had told her certain things in regard to her sickness, and that three ladies had told her that they had suffered just exactly as she had. (All of which statements were false.) On her journey to the hospital she told about being able to see Christ, and told about carrying on conversations within her head with Him. There was no history of any polyneuritic symptoms.

On admission, the patient was apathetic and listless, but talked freely, and answered all questions quite promptly and relevantly. She complained of a spinning sensation, and a feeling of pressure in her head, which seemed in some way to affect the nerves of her eyes; she said that she could not read; could not develop any interest in anything, and felt as if she was a stranger to her self. She described many other curious sensations and feelings, *e. g.*, that her brain consisted of two parts, one normal and one abnormal, that there were obstructions in the blood-vessels of her brain. One of the most peculiar of her symptoms was a pseudo-hallucinatory state in which she saw the figure of Christ, and at other times had visions of beautiful forests, knights, and gay people. In reference to these things she would say: "It is all a figment of the brain I suppose, but it is just as real as my being here talking to you now." In addition to the

visions, from time to time she would seem to hear a voice telling her to "be comforted," and that also she clearly recognized as being "purely a mental thing—a thought." At first she was correctly oriented for time and place, but it was very striking to notice how poor her memory was for the names of persons, and her total inability to give an idea of the onset and course of her sickness, and of events immediately preceding admission. The later period of her gestation was apparently almost a blank to her. She did remember that her baby had been born towards the end of March, 1913, but absolutely denied that there had been anything wrong with her in any way until six weeks after its birth. She had no idea, for instance, that for several months she had been nourished almost entirely by rectal enemata; she could not tell when she had come to Baltimore (three days previous to her admission); could not tell what hotel she had stayed in, and did not remember her examination by a neurologist. She had entirely forgotten a name, address, and color, after four minutes. Her memory for remote events, and her grasp on matters of general intelligence were well retained. She had a very good realization of and insight into her condition, frankly admitting that her memory for recent events was poor, and that her pseudo-hallucinatory state was due to her imagination and general nervousness.

Physically, the patient was a well-nourished woman, who showed no disease of the internal organs. Her sense of smell was defective on both sides, as she could not recognize cloves, peppermint, or whiskey. Otherwise, there were no neurological signs. Her pulse, temperature, and respiration rate were normal.

Following Admission.—During the whole period of the patient's hospital residence she continued to present almost the same picture as on admission. She had to have some one constantly with her trying to encourage, stimulate and employ her in every way, but despite the utmost help she would constantly complain of peculiar spells, in which she would close her eyes tightly and show facial grimacing. In these spells she would complain of something of the nature of an iron weight pressing against her brain, and would lose all use of herself. She suffered from sensations as if she were falling from a great height, and her pseudo-hallucinatory state remained constant.

The feature, however, which was of most interest in the case was her exceedingly poor memory for recent events, and her defective power of retention. Her retention was tested by means of giving her three different things to remember, by short stories, by word-pairs, and repetition of numerals; with all of these gross defects were easily elicited. In addition to these defects, a good idea of her state of mental confusion may be gotten from the following facts: One morning she put on her dress before her undergarments; another time she put two dresses on; she was occasionally unable to find her own room on the ward; she would not infrequently after a bath start to put her clothes on without drying herself. She, also, during her hospital residence, became disoriented for time, could never tell the day, date, or month, and was uncertain as to whether the year was 1913 or 1914. An attempt was made to benefit the patient's condition by means of thyroid extract medication, but no benefit resulted. The patient was discharged on April 12, 1914, in an unimproved condition.

In this case, then, we have a woman 37 years old, who up until the onset of her present sickness seems to have been healthy and normal in every way. In all three previous pregnancies we have a history of vomiting of short duration. During her last (fourth) pregnancy, however, uncontrollable vomiting apparently played such a role that the patient became emaciated, and during the last two months of gestation developed a psychosis characterized by apathy, forgetfulness, suspiciousness, and then later by a peculiar pseudo-hallucinatory

state, and a tendency to fabricate. During her hospital residence her mental confusion, her exceedingly poor power of retention, her disorientation for time, and her pseudo-hallucinatory state were the outstanding features.

How are we to interpret such a condition? From the point of view of symptomatology many of the symptoms might tend to make one think that here we are dealing with a case of dementia præcox, and that the pregnancy was merely incidental. In support of such a view the apathy and listlessness, the peculiar ideas, such as one part of her brain being normal and the other abnormal, and the pseudo-hallucinatory state would be advanced. After all, however, the point which impresses one most is her extraordinary defect in memory and in power of retention, and that associated with good insight into her condition is so foreign to the types of dementia præcox that we know as alone to be almost sufficient to rule out such a diagnosis. The explanation that I feel justified in putting forward is that here we have an individual who, on account of the uncontrollable vomiting of pregnancy, became so emaciated and exhausted that definite organic changes resulted, in consequence of which a specialized portion of her memory became deeply affected. With such a lowering of the general level, it seems to me quite understandable why the psychogenic material which no doubt has been dormant in the patient should be expressed. This case, as far as a fairly thorough review of the literature has taken me, seems to be unique, but is in harmony with Korsakow's original observation that "*polyneuritic symptoms need not be a constant accompaniment of the psychosis.*"

Furthermore, this case corresponds to those of the toxic-infectious group which Hoeh has designated by the term Amentia. In connection with his cases Hoeh has emphasized the fact that Freudian mechanisms undoubtedly play an important role, but do not alter the main facts of the clinical picture.

Before attempting to draw any general deductions from these two cases, it would seem well to consider some of the cases described by others, so as to see whether we can get at any factors which are more or less constantly present. I want especially to direct attention to those cases which have shown a Korsakow's symptom-complex, and to those with a generalized neuritis, but without any mental symptoms. I have already made mention of Boulton's case, and of the cases described by Churchill, Möbius, and Korsakow.

Madge in 1871 reported the case of a multipara, 36 years, who at the fourth month of her third pregnancy started to suffer from severe pains in her hands and feet, which became exceedingly sensitive and painful. Later the patient developed an anæsthesia and complete paralysis of her hands and feet. In this case the patient's mind is stated to have been confused, and her memory was impaired. Under electrical treatment improvement occurred in her general condition. It is very interesting to note that about one year after her illness had started the patient was delivered of a dead fœtus of about four months, which to all appearance had been retained in the uterus for many months.

Whitfield's case.—A multipara, 40 years old, on August 7, 1888 gave birth at full term to her seventh child. From the beginning of her pregnancy the patient had suffered from uncontrollable vomiting, on account of which she lost about 80 pounds in weight. Two weeks previous to her confinement her legs felt cold, she partially lost the use of them, and had to be assisted up and down stairs. The day after labor vomiting ceased, but she soon started to complain of pain and "pins and needles" in her legs, and thirteen days later had almost lost the entire use of her arms and legs. Pain was easily elicited on deep pressure over the nerve trunks. The knee-jerks and other tendon reflexes were absent.

The case described by Desnos, Joffroy, and Pinard, again emphasizes the important part played by uncontrollable vomiting in the development of such states.

A multipara, 41 years, had had two previous pregnancies, and was in an anæmic condition. During her third pregnancy the uncontrollable vomiting was alarming, and at the end of the fourth month the lower limbs were markedly atrophied, and this was followed two or three days later by an atrophy of the arm muscles. There was no reaction of degeneration, no disorder of sensibility, and no loss of sphincter control. There was a marked diminution of the patient's intellectual power, especially of her memory. Artificial abortion was performed, and was almost immediately followed by a betterment of the patient's condition. Function finally returned to the muscles and the patient was cured.

Polk, under the title "Mania and Multiple Neuritis in Pregnancy," described a case which terminated fatally at the fifth month. The term "mania" is apparently used by Polk as synonymous with "excitement," because there is nothing at all in the description of the case to make us think of a manic-depressive excitement. On the other hand, the mental condition as described by Polk seems to have consisted essentially of a delirium with fear reaction, and a poor memory for recent events. The case indeed is very similar to the first one reported by me in this paper.

A multipara, 28 years, during the second month of her second pregnancy started to suffer from nausea and vomiting, on account of which she became markedly emaciated. At the fourth month of gestation the vomiting ceased. At this time the patient became delirious and excited, talked in an incoherent way, and seemed to have no realization of her condition or surroundings. She thought that there were gloves on her hands, and asked to have them pulled off, and expressed many rapidly shifting "delusions." She soon forgot every statement made to her. Associated with this mental condition, there was paralysis of both the flexor and extensor muscles of the hands, entire loss of grip, atrophy of the forearms, paralysis of the muscles of both legs with foot-drop, some movement in the thighs, but none in the toes or feet. She complained of various paræsthesias and tenderness was easily elicited on pressure of the muscles. There was involuntary micturition. The respiratory muscles next became affected, and death resulted at the fifth month.

In Handford's three cases the paralysis came on immediately

after confinement; the third one should probably be ruled out altogether, as not belonging to this class of cases. In none of the three cases have we any mention of the mental condition of the patient.

CASE 1.—Multipara, 43 years, three days after confinement lost the power in her legs completely, had the sensation of "pins and needles" in the arms, a short time later paralysis of the arms. The muscular sense became impaired, there was impaired cutaneous sensibility, and greatly increased deep sensibility; knee-jerks were absent, the reaction of degeneration was present in both arms and legs. In twelve months the patient was comparatively well.

CASE 2.—Woman, 34 years, had complete paralysis of extensors of toes and flexors of ankles, with weakness of most of the other muscles of the legs coming on immediately after confinement. There was both superficial and deep hyperæsthesia; no contraction in the muscles below the knee to strong faradic stimulation. Complete recovery resulted.

CASE 3.—Multipara, 31 years, immediately after confinement complained of difficulty in walking and weakness in her arms. The knee-jerks and superficial reflexes were absent, and the cutaneous sensibility was diminished in her arms and legs. In addition, she had a double ptosis, a divergent strabismus, and a complete internal ophthalmoplegia in both eyes. Her optic discs were normal. After a period of five years the patient's condition was unchanged.

Korsakow and Serbski have described a case with antopsy, in which well-marked degenerative changes were found in the peripheral nerves, especially in the most distal nerves, *e. g.*, dorsalis pedis. The other nerves most affected were the median, ulnar, phrenic, abducens, acoustic, and vagus. In the spinal cord an increase of connective tissue was found in the columns of Goll, and in the lateral columns, especially on the right side. No pathological changes were found in the brain. The patient was 27 years old, and at the fourth month of an extrauterine pregnancy started to suffer from vomiting. The case was complicated by a parametritis, and an abscess in the iliac fossa. She was forgetful, confabulated, had a retention defect, was dull and tearful, and had visual hallucinations. The muscles of the legs and arms were weak, pain was elicited on deep pressure, but the knee-jerks were retained. Her pulse was 140 per minute.

Another case with autopsy has been reported by Solowieff. This case in contrast to most of the others occurred in a primipara. The patient was 24 years old, and at the third month of her pregnancy was in a very poorly nourished condition, owing to persistent vomiting. She became restless, suffered from headache, and paræsthesias of the lower extremities, which were sensitive. She became unable to walk, the knee-jerks were lost, pain was elicited on deep pressure, and the reaction of degeneration was present. Later the diaphragm became weak. Her pulse varied from 130 to 160 per minute. Mentally, she is described as having been delirious and very forgetful. At autopsy degenerative changes were found in the phrenic, peroneal, median, and vagus nerves.

Lunz has described a case in which, owing to an early involvement of the cranial nerves, the similarity of the condition to a diphtheritic paralysis is emphasized.

A woman, 24 years old, gave birth to a weakly child, which died after two weeks. A short time later the patient experienced difficulty in swallowing and choking; then diplopia and dizziness developed. First the right hand felt dull, later the left hand and arm, and later still the lower extremities. Gradually, the swallowing difficulty became worse; slight weakness showed itself in both sixth nerves; slight paresis of the left side of the face, the tongue was protruded to the left, and the palate was not well elevated on phonation. She developed a *main-en-griffe* on the left side, became unable to walk more than a few steps, and pain was elicited on deep pressure of the muscles. The triceps jerk was absent on both sides, but the other tendon reflexes in the arms were retained; the knee-jerks were absent; the electrical excitability was diminished.

One of the most important series of cases (4) has been published by Eulenburg:

CASE 1.—One-sided neuritis, with atrophic paralysis in the median and ulnar spheres. The patient was a primipara, 28 years, who ten days after labor experienced severe diffuse pain in the left arm, paralysis and atrophy, which, after a period of two months' treatment with massage, cleared up.

CASE 2.—A case of neuritis of the right tibial nerve with subsequent recovery. This case was associated with vomiting.

CASE 3.—One-sided neuritis in the region of the right sciatic nerve. The affection started at the end of the first week of the puerperium. This case likewise was associated with vomiting.

CASE 4.—A multipara, 27 years, who during her second pregnancy had to have an abortion performed at the fourth month on account of severe vomiting. Eight days later she had the feeling that the lower part of the body was paralyzed. She next suffered from severe pain, and in 24 hours there was complete paralysis of the legs, then paresis of the arms, the back muscles, and finally aphonia and paralysis of swallowing, all in the course of 48 hours. During the course of the next eight days she became insensitive and confused. After several weeks the aphonia and difficulty in swallowing disappeared, the motility returned to the arms in the shoulder and elbow regions, but the fingers and hands, as well as the lower limbs, remained completely paralyzed. Pain was elicited on deep pressure of the muscles; at first there was some superficial sensory disorder, but later very little. The knee-jerks were absent on both sides; the reaction of degeneration was present.

In most of the cases so far referred to uncontrollable vomiting has been a prominent feature, but Elder has reported two cases, neither of which suffered from vomiting.

The patients were multiparæ, and in each the symptoms started about the sixth month of pregnancy. The symptoms started with tingling and paræsthesia, chiefly in the hands, but also in the feet. There was little or no paresis, but sensation was affected in both cases. In both cases alcohol, diphtheria, glycogenia, and lead could be ruled out. After delivery the improvement in both cases was rapid. Butler's case followed delivery, but from the description there can be little doubt about the diagnosis.

A married woman, 37 years, had at the fourth month of pregnancy a still-born child. Three weeks later she developed a "milk leg" on the right side, suffered from vomiting, and started to fall off in weight. Later she lost power in both legs; numbness and tingling developed in the hands and arms, which

was later followed by weakness. On examination there was marked atrophy of all the muscles of the upper and lower extremities, and also of the trunk muscles. The knee-jerks were absent; tenderness was elicited on deep pressure of the muscles. The electrical reactions were impaired. Improvement occurred under massage and general measures.

One of the best and most comprehensive articles on this subject is that of Reynolds, who in 1897 gave a general summing up of the known facts, and described one personally observed case.

Primipara, 24 years, when four months pregnant, was suffering from such severe and uncontrollable vomiting that an abortion had to be procured. Following the abortion, the patient suffered from complete loss of sphincter control for two or three weeks. About a month after the abortion her feet felt cold and numb, and a month later still her legs were very weak, and sensation in them was almost entirely abolished; there was no affection of the upper extremities. Finally, she could not stand or walk; her knees were contracted, and the knee-jerks could not be obtained. The patient improved under massage. Two years later the patient had a successful second pregnancy without vomiting, and without untoward results.

Saenger's six cases are also all interesting, in that they all developed after an apparently normal labor.

CASE 1.—A woman, 36 years, on February 12, 1896, had a normal labor. Previous to the birth the patient had experienced some weakness and tingling in the left arm, and occasionally feeling of pain. Shortly after the birth a dull feeling, weakness, and some pain developed in the right arm. After some days there was complete paralysis of both arms and legs; pain was elicited on deep pressure over the nerve trunks; the tendon reflexes were absent. Later weakness developed in the diaphragm and back muscles; transitory swallowing difficulty, and rectal paralysis; the bladder was not affected. A partial reaction of degeneration was elicited in the tibialis anticus, and in the peroneal muscles. By Christmas, 1896, the patient was completely well.

CASE 2.—A woman, 30 years, several weeks after a normal labor and puerperium developed an acute generalized polyneuritis of the nature of a Landry's paralysis. There was a transitory rectal paralysis. Sudden death resulted. No changes were found in the cord or brain. A well-marked degenerative neuritis was found in the peripheral nerves, and also in the vagus nerve.

CASE 3.—A woman, 34 years, had a normal labor, and no fever during the puerperium, but developed a dull feeling in her fingers, and then weakness in both legs. There was some pain and tenderness of the bladder. Soon there developed complete paralysis of both the upper and lower extremities, pain was present on deep pressure of the muscles, slight cutaneous sensory disturbance, and absence of the tendon and skin reflexes. The reaction of degeneration was elicited in the small muscles of the hand, and in the calf muscles. Complete recovery resulted after a period of four months.

CASE 4.—A woman, 32 years, five days after labor developed paresis of the left median and ulnar nerves. The patient recovered in a few weeks.

CASE 5.—A woman, 28 years, ten days after labor developed pains in her legs, and then in the arms. After some days there was a neuro-myositis of the right radial and median nerves; after some weeks the same affection occurred in the left arm, but to a lesser degree. This patient also recovered.

CASE 6.—A case of double-sided retro-bulbar neuritis.

In none of these cases, with the possible exception of the last, was there any suspicion of a febrile process.

Danziger's case is in many ways similar to that of Lunz, and is of interest, owing to the early involvement of the cranial nerves. A primipara, 21 years, 14 days after normal labor experienced difficulty in swallowing. On the next day there was hoarseness, twitching of the face, and general pain. The soft palate was only very slightly raised on phonation, the speech was nasal, and in swallowing fluid was regurgitated through the nose. The right vocal cord was in a cadaveric position. The arms and legs were weak, and pain was elicited on pressure. The knee-jerk was absent on the right, and diminished on the left side. A gradual recovery resulted.

A most interesting case with autopsy has been described by James Stewart. A multipara, 33 years, about two months previous to confinement started to experience numb feelings in her limbs. In the previous pregnancies she had suffered from severe vomiting, and in this last pregnancy the vomiting was so severe that for six weeks she was confined to bed. She was emotional, but otherwise her mental condition is described as normal. About nine weeks after labor she showed considerable loss of power in the muscles of both lower limbs, but in no single muscle, or group of muscles, did it reach an absolute degree; it was distinctly more marked in the most peripherally situated muscles. In both upper limbs a similar, but less marked paralysis was present, being also more marked in the distal parts. There was, however, no definite foot-drop or wrist-drop. The feeling of numbness in the lower limbs and abdomen extended up to the eleventh thoracic segment, and in the arms it extended up to a point midway between the elbow and shoulder. Touch was diminished over the numb areas; pain and thermal sense were unimpaired. The calf muscles were very tender on pressure, the knee-jerks were normal, and the electrical reactions were not disturbed. The pulse was rapid varying from 80 to 120 per minute; the respiration rate was from 24 to 30 per minute. The urine at all times was free from any abnormal ingredients. Later there was complete wrist- and foot-drop, and the knee-jerks became lost. Later still the diaphragm became paralyzed, and death finally resulted from pneumonia.

The examination of the nervous system was made by Dr. Shirress. The brain, spinal cord, and ganglia, were removed; also both sciatics, musculospirals, anterior crurals, peroneals, anterior tibials, pneumogastrics, and phrenics. Microscopically, the peripheral nerves by Marchi's method showed the signs of a true parenchymatous degeneration, the hæmotoxolin and Van Gieson's method revealed also a marked interstitial inflammation, the blood vessels being distended with numerous hæmorrhages in the epi- and endoneurium. The pneumogastric and phrenic nerves showed more of a parenchymatous condition than interstitial changes. In the cord a scattered degeneration was found in the posterior columns. Degenerated fibers were also found in the lateral region of the cord (direct cerebellar tract) in the upper dorsal and cervical segments. The posterior roots were degenerated along the whole length of the cord. No changes were found in the anterior roots.

Marked and advanced chromolytic changes of the peripheral, central, and perinuclear varieties were found in the ganglionic cells of the gray matter in the anterior horns, and in Clark's column. The most marked changes were found in the fifth, sixth, and seventh cervical segments.

Other cases with autopsy reports have been described by Mader and Lindemann. Mader's case was associated with persistent vomiting, and at autopsy extensive neuritic changes were found in the sciatic, tibial, and peroneal nerves; the cord was not involved. In Lindemann's case, in addition to there being a parenchymatous neuritis, degenerative changes were also found in the liver and kidneys. Still another case with autopsy has been reported by Dustin:

A multipara, 30 years, at the sixth month of the last pregnancy suffered from uncontrollable vomiting. Following the birth of a macerated foetus a quiet delirium set in without fever. She developed pain in the left leg, which became contracted; and lost control of her sphincters. Her pulse varied from 100 to 108, and her breathing was above 30 per minute. The leg muscles became atrophied, pain was elicited on deep pressure, and the knee and Achilles jerks were absent. At the autopsy degenerative changes were found in the crural and sciatic nerves. At the third lumbar segment of the cord there was chromolysis and vacuolation of the anterior horn cells. The anterior and posterior roots were normal.

In 1913 Hahn described a case which clinically was similar to that of an alcoholic Korsakow psychosis:

A multipara, who three years previously in the third month of pregnancy had suffered from severe vomiting, and had two epileptiform attacks. During the last pregnancy vomiting again started during the third month, then nystagmus developed, and the pulse became above 100 per minute. An artificial abortion was performed, which stopped the vomiting, but the general condition of the patient was not improved. The patient became very dull, the nystagmus became more marked, a retinal hæmorrhage occurred, both legs were paralyzed, the patellar reflexes were lost, and there was a sphincter paralysis. All these severer symptoms occurred about 12 days after the artificial abortion.

Mentally, the patient at first was dull and confused, but later a delirious condition developed, in which she thought that she held her baby in her arms, kissed it, and showed it to the other patients. After the acute stage had passed the patient lapsed into a state of mild euphoria with spells of irritability, had an exceedingly poor power of retention, and an amnesia for her hospital residence. In the course of eight months her power of retention showed considerable improvement.

Before concluding this review of the literature, I would just like to mention the cases and communications of Hösslin, Dufour and Cottenot, Stelzner, Burr and McCarthy, Craik, Cross, Buzzard, Aldrich, Borham, Köster, Johannsen, and Bernhardt.

GENERAL CONSIDERATIONS.

It is an accepted and well-known fact that the equilibrium of health is more apt to be disturbed during pregnancy than at almost any other time. Wright believes that during pregnancy there is a general systemic toxæmia, due to the more or less faulty action of the liver, intestines, and kidneys, and toxins can be found chiefly in the blood, liver, and muscles.

Wright emphasizes the fact that the slightest departure from health during pregnancy should make one suspect a toxæmia, and some of the symptoms he lays stress on are: salivation, disorders of digestion, and constipation, general malaise, anæmia, nervous disturbances with headache, disorders of vision, irritability, deficient urine excretion, and albuminuria. Bouffe de Saint-Blaise (quoted by Hösslin), in considering the toxins of pregnancy, has also emphasized the changes in the liver and kidneys, and his work, of course, is of particular interest in relation to Lindemann's case, where there was not only a parenchymatous neuritis, but also degenerative changes in the liver and kidneys.

Eulenburg, in common with most others, believes that some cases, although only observed during the puerperium, are in reality cases of the neuritis of pregnancy, and he advanced the hypothesis that impaired gastrointestinal functions during the gravid period led to an autointoxication through the formation in the gastrointestinal tract of some substance—possibly acetone—which is absorbed, and causes the neuritis.

Reynolds had the idea that persistent vomiting set up an acetonæmia, and that acetone, or some allied product, produced the neuritis, just as may happen in the neuritis of diabetes. So far, however, no evidence has been produced to substantiate the acetone theory, and we have no knowledge of the nature of "the toxin" which is supposed to be responsible for the condition.

The relation which hyperemesis gravidarum bears to the condition seems to be a close one, especially in those cases which show a generalized type of neuritis. Bayle has even gone so far as to say that the generalized forms only occur after severe cases of hyperemesis, and it was no doubt on account of the same supposition that Clifford Allbutt believed that the vomiting and the neuritis were due to the same toxin. A number of cases, *e. g.*, those of Lunz, Saenger, Korsakow, Danziger, and Elder, have now, however, been described in which no mention is made of the occurrence of hyperemesis gravidarum, and therefore Allbutt's and Bayle's supposition can hardly hold good. But from the very frequency of its occurrence there can be no doubt that hyperemesis plays a most important role, whether or not it is from the hyperemesis *per se*, or from the fact that the hyperemesis is responsible for causing a general exhaustion of the patient, thus rendering the patient more susceptible. Out of 92 cases of all grades of the neuritis of pregnancy collected by Hösslin, hyperemesis gravidarum was present in 19. Hösslin, however, remarks that this number assumes much greater proportions when it is stated that the cases of neuritis which gave a history of hyperemesis were much the most severe. Out of 46 cases in which all the extremities were paralyzed, hyperemesis was present in 16, while in the anamnesis of 37 cases where only the facial nerve, or one, or only the upper extremities were involved, hyperemesis was not reported. According to Hösslin, the fact that the hyperemesis is associated with the more severe cases is proof positive against the hysterical nature of the vomiting, and he conclusively states that he knows of no case of hysterical vomit-

ing in a non-pregnant woman associated with polyneuritis. Since Hösslin's article was published a number of other cases have been reported, *e. g.*, those of Dustin, Dufour and Cottenot, Hahn, and the two which are the subject of this paper, and in all of these cases persistent vomiting seems to have been an important factor.

In addition to the hyperemesis, the weak, exhausted, emaciated, condition resulting from it, the retention of a macerated foetus, the retention of placenta, and the involution of the uterus, have all been supposed to have played a part. At present, however, we must content ourselves with the summing up of Aldrich, and say that the condition is one which usually occurs in women exhausted from vomiting, and that probably some toxin is formed within the body of the mother or child which has a selective action on the nerve tissue of the pregnant woman.

Another point which may be emphasized is the much greater frequency with which multiparæ are affected as compared with primiparæ, the reaction apparently being in the nature of an anaphylactic phenomenon.

The indications and the time for the production of abortion are questions for the obstetricians, but it may be well to remark that most of the French observers state that when the pulse increases to 100 or over per minute an abortion should be immediately produced. The points, however, which I especially wish to lay stress on are:

(1) The pregnant state must in certain cases be recognized as an important etiological factor in the production of peripheral neuritis, and of that condition known as Korsakow's syndrome.

(2) The neuritis caused may be either (1) local, *e. g.*, affecting one nerve or one limb, or (2) diffuse, *e. g.*, affecting all the limbs, and certain of the cranial nerves.

(3) The mental disorder characteristic of the condition is usually associated with a generalized polyneuritis, but, as evidenced by one case reported here, it may occur alone.

(4) The frequent history of hyperemesis gravidarum in association with the generalized forms of the disorder is so striking that it suggests a possible line of approach as to the elucidation of the nature of the toxin.

(5) Those patients who in previous pregnancies have suffered from severe vomiting, or other serious toxic phenomena, should be strongly urged to avoid any further pregnancies.

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OBSERVATIONS UPON THE BACTERIA FOUND IN MILK HEATED TO VARIOUS TEMPERATURES.

By W. W. FORD, M. D., and J. C. PRYOR, M. D.

(From the Laboratory of Hygiene and Bacteriology, Johns Hopkins University.)

More than twenty-five years ago Flügge,¹ then Professor of Hygiene in the University of Breslau, pointed out the important fact that milk heated to various temperatures always shows, upon incubation at 22° C. or at 37° C., a bacterial growth due to the presence in the milk of heat-resistant spores. This was equally true of boiled milk or of milk exposed to the lower temperatures employed in pasteurization. Dependent upon the kind of bacteria developing, Flügge differentiated two sorts of decomposition which might occur, one explosive and caused by gas-producing anaerobes, and one consisting of a slow liquefaction of the proteids in the milk and due to peptonizing aerobes. To the latter group Flügge attributed particular significance, since the changes produced by such bacteria in the milk were slow and easily overlooked, and yet the milk might be full of microorganisms. He therefore raised the important question as to the rôle which these bacteria might play in the production of the summer diarrhoeas of children. Under ordinary circumstances the spore-bearing organisms in milk would be restrained by the growth of the lactic acid organisms and only in milk heated to a temperature sufficient to destroy the latter group could the former group (spore-bearing bacteria) develop in such profusion as to change the character of the milk or offer any danger to children. According to Flügge, the spores of the peptonizing bacteria would resist the action of the acid gastric juice and find the proper conditions for development in the lower bowel, where they would multiply and elaborate the poisonous products which give rise to the grave symptoms of intoxication seen in summer complaint. The various microorganisms isolated by Flügge from heated milk were later studied by Gotschlich and Kaensehe. The *Bacillus butyricus* of Hueppe was the principal anaerobe and species usually classified as "subtilis" or "mesentericus" forms (*Bacillus subtilis*, *Bacillus mesentericus vulgaris*, *Bacillus mesentericus fuscus*, etc.), were the most important aerobes.

This elaborate investigation of Flügge has received little or no attention from American physicians, far less indeed than work of such a fundamental importance deserves. As far as we can learn, there has been no particular effort made to determine whether Flügge's conclusions in regard to the presence

of peptonizing aerobic bacteria in milk can be applied to this country, although H. R. Brown² in Dr. Theobald Smith's laboratory has described a variety of anaerobes which occur in the milk in Boston. Dr. Letehworth Smith³ also, in the Department of Health in New York, has studied the properties of some two hundred organisms isolated from the milk in that city, but not with the particular object of differentiating between the species found in raw and cooked milk. In the many valuable American studies upon the pasteurization of milk, especially those of Rosenau,⁴ Jordan,⁵ and Ayers and Johnson,⁶ Flügge's work has received comparatively little attention, and yet it is probably the most important single investigation upon this subject that has ever been published. For if it be true that milk always contains bacterial spores capable of resisting a high temperature, even that of boiling, and of giving rise, by their multiplication, to putrefactive changes in the milk, this is a fact of far-reaching importance which should never be lost sight of in any consideration of the problem of pasteurization.

Finally, the contention of Flügge that spore-bearing, peptonizing bacteria play a rôle in the summer diarrhoeas of children has never been seriously considered here. The general opinion in regard to this work may be indicated by quoting the opinion of a leading writer in this field who states that "this view (*i. e.*, that spore-bearing bacteria survive pasteurization,) started with the work of Flügge and has gradually lost ground for lack of clinical and laboratory confirmation" (Rosenau⁷).

In view of the importance of this question, both from the theoretical and practical standpoint, we have made the attempt to repeat Flügge's work during the past eighteen months in the hope of determining whether his conclusions are applicable to this country. The samples of milk have been collected in Baltimore and Washington, in all about 129 specimens being studied. The results of the examination of the milk in Baltimore only will be reported in this paper, the Washington samples being reported upon by one of us in another paper.

TECHNIQUE.

The milk sold in Baltimore may be divided roughly into dipped milk and bottled milk. The dipped milk is sold very

largely in the poorer sections of the city, especially in the small shops and corner groceries. Its content in bacteria is uniformly high, as has been indicated elsewhere.⁸ The bottled milk is of a much better character, the bacterial content usually low and a certain proportion is pasteurized, but not, however, under city control.¹ No certified milk is delivered in Baltimore, but a Walker-Gordon milk of exceptional purity is sold very largely. The milk here is obtained from a large area of farming land in Maryland and Southern Pennsylvania.

Altogether 78 samples of Baltimore milk, representing 21 different dairies, were employed in this investigation. The dipped milk was collected in the small shops, transferred to sterile pails or flasks and carried to the laboratory, while the bottled milk was delivered directly in the original containers. Considerable care was exercised to obtain milk from a variety of sources to give results which may be said fairly to represent Baltimore conditions. In consequence, the specimens taken represent nearly every kind of milk sold in the city. All the samples of milk examined were subjected to the same treatment. Flasks, varying in capacity from 250-500 cc., were either filled with the milk up to the neck so that the layer of cream should form a plug and produce anærobic conditions at the bottom or were about half filled so as to offer a wide area for oxygen absorption and give satisfactory aerobic conditions. These flasks were heated on the water bath to various temperatures for varying periods of time, care being taken to immerse them to such a depth as to insure the proper heating of the milk itself. All specimens were immediately incubated without cooling at either 37° C. or at 22° C. Raw controls were always carried along at the same temperature. After the lapse of 48-96 hours, when the bacterial changes had fully developed and the characteristic reactions were seen in the milk, agar plates were poured for the cultivation of the aerobic bacteria and rabbits were inoculated in the ear vein with cubic centimeter quantities for the isolation of *Bacillus ærogenes capsulatus* of Welch and Nuttall (*Bact. Welchii*). No attempt was made to work out the many other anærobes which must be present in Baltimore milk, attention being paid only to the "gas bacillus" as giving us the most convenient method of determining the presence or absence of anærobic putrefaction. This organism was always sought for by the method of rabbit inoculation, the lesions found in this animal being regarded as essential in its identification. In general the extent to which the flasks were filled made no appreciable difference in the reactions shown by samples of milk heated to the higher temperatures, but apparently milk heated to 60-65° C. may undergo a variety of changes, depending upon several factors, of which one is the size and shape of the container. This point was not clear by any means, and is still the subject of study by us. The different controls of raw milk behaved in much the same way, the milk labeled pasteurized showing a fairly high bacterial count and acidifying and clotting normally. These latter specimens have not therefore

been given separate consideration. Particular attention was paid to the reactions shown by raw milk, by milk heated to 65° C., to 85° C., and by boiled milk.

REACTIONS OF RAW MILK.

All the samples of Baltimore market milk, both raw and that labeled "pasteurized," when incubated at 37° C. or kept at 22° C., exhibited changes which did not differ from those seen in milk in other localities. Within 24 to 48 hours in the thermostat and 48 to 72 hours usually at room temperature the milk was acidified and firmly clotted. Cultures taken within the first few days revealed as the predominant species the organisms first accurately described by Gunther, Thierfelder and Leichmann, and which are known by several names, such as *Bacterium lactis acidi*,⁹ *Streptococcus lacticus* and *Bacterium Güntherii*. As Shippen has pointed out, the latter designation, *Bacterium Güntherii*, was given this species by Lehmann and Neuman¹⁰ and should be retained in accordance with the rules of priority in botanical nomenclature. *Bacillus lactis ærogenes* and *Bacillus acidi lactici* stood next in point of frequency, but were by no means common, while *Bacillus coli* was an exceptional isolation. Pigmented organisms were also rarely encountered. Spore-bearing bacteria were almost never found in plates poured during the first few days.

Rabbits inoculated for the isolation of *Bacillus ærogenes capsulatus* were at first uniformly negative, even when the spores of the organism were present in the original milk and it could be obtained on cultures by subjecting the milk to a temperature of 85° C. (see below). Various methods of isolating it were tried. Rabbits inoculated in the ear vein with 1 cc. quantities of whey and then killed and kept in a warm place did not show the characteristic gas œdema, nor could it be obtained on cultures from the blood stream or from the organs. Transfers of whey in 1 cc. quantities to sterile milk tubes which were then heated to 85° C. and incubated anærobically were also without result, the tubes never revealing the gas bacillus reaction. Finally rabbits inoculated with 1 cc. quantities of whey heated to 85° C. to destroy all vegetative bacteria were likewise negative. It was evident that clotted raw milk does not furnish a medium favorable for the survival and development of the gas bacillus, possibly because of its high degree of acidity or possibly because of the many other organisms present. In our first series of six milks the organism was never obtained from raw milk allowed to clot, no matter what method was used. Later, in a second series of six, it was obtained in two cases when the whey was examined early, within the first 48 or 72 hours. Rabbits inoculated with small quantities, killed and kept at 22° C., exhibited an extensive gaseous œdema of the subcutaneous tissues, gas in the fascias between the muscles, gas bubbles in the heart and larger vessels and the characteristic reaction in the liver, the substance of which was riddled with gas blebs. Smears made from the blood and from the juice of the various organs revealed an encapsulated Gram-positive bacillus and transfers to litmus milk and agar

¹ Since this work was completed the Commissioner of Health of Baltimore City, Dr. Gorter, has been enabled to employ a force of inspectors for the milk-pasteurizing plants in the city.

showed the organism of Welch and Nuttall, usually in pure culture.¹¹ The survival of the gas bacillus in raw milk allowed to clot was evidently the exception, however, and not the rule.

Aerobic cultures from specimens of milk allowed to stand some days continued to reveal only the lactic acid organisms above mentioned with an occasional *Bacillus coli* or *Bacillus lactis aerogenes*. There was no particular increase of spore-bearing bacteria. Eventually very old milk specimens, kept six to eight weeks, showed an abundant surface growth of molds and pigmented species and some softening of the clot. A definite peptonization did not often occur. Occasionally foul odors developed in this very old milk, arising possibly from the multiplication of *Bacillus coli*.

REACTION AT 65° C.

Milk heated to 65° C. for 30-35 minutes and then incubated at 37° C. exhibited a reaction which may be regarded as characteristic. Within 24-48 hours it was rather firmly clotted, but the curd did not seem, as a rule, to be so abundant as that in normal raw milk, and in addition it was riddled with gas bubbles. Immediately after the clot was formed softening or peptonization of this clot set in, the gas bubbles being liberated and the milk being converted into a thin whey in which the curd was eventually completely dissolved.

Sometimes the reaction could properly be described as explosive, so violent was the evolution of gas, but in general the reaction seemed to consist more of a gaseous clotting followed by a rapid peptonization. Kept at room temperature the 65° C. milk revealed almost the same changes as were seen in the samples kept at 37° C., but the evolution of gas was not so marked and the peptonization was somewhat less rapid. The end-products were in all cases the same, however, the milk being converted into a thin watery fluid almost completely devoid of grosser particles of whey. Normal clotting without peptonization was extremely rare in milk heated to 65° C. for this length of time. In a series of 18 samples of milk, it occurred but once, the other 17 samples clotting and completely peptonizing.

Aerobic cultures made the first 48 hours to 72 hours revealed a variety of microorganisms the relationship of which to each other and to the organisms found in raw milk is somewhat difficult to determine. Sometimes the only colonies present were spore-bearing bacteria, even the small pin-point colonies seen with a hand lens developing into such species. These were transferred and identified as accurately as possible with our existing knowledge of the non-pathogenic spore-bearers. They belonged to the groups usually called *Bacillus subtilis*, *Bacillus mesentericus* and *Bacillus cereus*. In addition a spore-bearing organism which has the property of acidifying lactose and acidifying and clotting milk was obtained on a number of occasions. This will be described later in a paper dealing with the spore-bearing bacteria in milk. At other times the plates showed an abundant development of lactic acid organisms, these being even more numerous than the sporulators. Despite this discrepancy the milk samples went on to complete liquefaction. How far a temper-

ature of 65° C. will destroy vegetative bacteria is by no means clear. In our experience lactic acid organisms survive this temperature in a certain proportion of cases and this has been also the experience of Rogers,¹² Ayers and Johnson, Russell¹³ and a number of others who have called attention to organisms which withstand pasteurization.

Bacillus aerogenes capsulatus could not usually be obtained from 65° C. milk, even when the milk showed an explosive reaction. Thus in 12 samples with this reaction the gas bacillus was found by rabbit inoculation in only two instances, in the other ten cases the rabbits showing no gaseous oedema and cultures failing to reveal the organism of Welch and Nuttall. In eight of these ten samples the gas bacillus was present in the milk, the samples heated to 85° C. revealing it in abundance. Thus 65° C. milk, like raw milk, does not offer suitable conditions for the multiplication of this species and the explosive reaction seen in milk heated to this temperature can hardly be attributed to it. What part other anaerobes play in the production of the reaction does not, of course, appear from our experiments, nor was it clear whether gas-producing aerobes were not also left behind. On the whole we were inclined to regard the reactions seen in 65° C. milk as due to the combined action of the lactic acid organisms, spore-bearing species, and either gas-producing anaerobes other than the gas bacillus or some gas-producing aerobes surviving the heating of the milk. In the hope of clearing up the doubtful points, a number of samples of milk were heated to 60° C. for various periods of time and aerobic cultures taken. The results varied widely. At times the samples of milk clotted normally and cultures revealed only the ordinary lactic acid bacteria with an occasional spore-bearer. At other times the samples showed an explosive reaction like that of 65° C. milk, while the clot which was formed was rapidly peptonized. In general, the reaction consisted of a rapid coagulation of the milk and a slow peptonization of the coagulum. Cultures from such milks revealed many of the sporulating organisms seen in 65° C. milk mixed with the lactic acid bacteria. The reactions in milk heated to 60° C. for 30 minutes did not differ especially from those seen in milk heated to 65° C., but the proportion of samples showing normal clotting was greater. Thus in 18 samples heated to this temperature 14 clotted and completely peptonized and four clotted normally without peptonization. In 12 samples heated to the same temperature for shorter periods of time, 10 and 20 minutes, three specimens clotted normally and here aerobic cultures showed only lactic acid organisms, while nine specimens clotted and peptonized. In general the samples of milk which showed a normal clotting at 60° C. or 65° C. were from better-grade dairies than those in which the clot was peptonized, but this was not a universal rule. The reactions of both 60° C. and 65° C. milk were by no means clear, and it was evident that they might depend upon a variety of factors. The age of the milk, the original bacterial content of the samples, the amount of contamination by spore-bearing bacteria, both aerobic and anaerobic, the shape of the container, all might be factors which played an impor-

tant part in determining the end-reaction. In short, milk heated to 60-65° C. is just on the border line and is capable of undergoing a variety of changes. Since this is the temperature of commercial pasteurization, it is hoped that future investigation will clear up some of these doubtful points.

REACTIONS AT 85° C.

Milk heated to 85° C. for 30-35 minutes and then incubated at 85° C. showed the same reaction in nearly all the samples examined. Within 12-18 hours it was firmly clotted and partially peptonized, with the active evolution of gas. The combination of these three changes gave the samples a characteristic appearance, which may properly be designated as violently explosive. The evolution of gas was frequently so pronounced as to force the upper layer or plug of cream out of the flask, the cotton stopper being carried with it and being deposited on the shelf of the thermostat some little distance from the flask itself. By the end of the first day the casein was often completely peptonized and by this time the evolution of gas had also usually subsided. Rarely the complete solution of the coagulum was delayed for 48 hours. Milk which has undergone this explosive reaction has the characteristic odor of butyric acid, which may give way to the disagreeable odor of putrefaction if the samples are kept some time.

This violent gas reaction with coagulation of the milk and complete peptonization may be regarded as typical of milk heated to 85° C. and then incubated at 37° C. It was obtained in all instances in a series of 72 samples of Baltimore milk, regardless of the source. Dipped milk from the corner stores and bottled milk of the better grades alike showed it. Occasional variations in the intensity of the reaction and the length of time required to bring it about were noted, but in all instances the end-result was the same, a complete liquefaction of the precipitated casein.

Aerobic plates made from 85° C. milk at various intervals, both early and late, revealed a host of microorganisms, all of which seemed to belong to the groups of sporulators mentioned above. Among them may be mentioned such species as *Bacillus subtilis*, *Bacillus mesentericus vulgatus*, *Bacillus cereus* and the spore-bearing coagulator already referred to. On no occasion did we obtain on our plates any lactic acid organisms or non-sporulating bacteria of other groups.

Rabbits inoculated with small quantities of whey (1 cc.) and kept in a warm place were nearly always blown up by the end of 18 hours and at autopsy showed the gaseous oedema characteristic of experimental inoculation by *Bacillus aerogenes capsulatus* (*Bact. Welchii*). The blood in the heart and larger vessels was permeated with gas bubbles and the liver was decomposed in the typical way. Smears from the blood and organs revealed the Gram-positive encapsulated gas bacillus and cultures on litmus milk and agar were also positive. The gas bacillus is probably always present in Baltimore milk and may be obtained by heating it to 85° C. and inoculating rabbits. In 30 consecutive samples showing the typical reaction rabbit inoculation gave characteristic appearances

in the tissues and positive cultures 25 times. In the 5 negative cases the animals were inoculated with milk more than four days old, suggesting that the organisms had died out or been overgrown by other species.

The changes seen in 85° C. milk may thus be said to arise from the combined action of aerobic spore-bearing bacteria and *Bacillus aerogenes capsulatus*. The latter organism is doubtless responsible for the violent evolution of gas and the former organisms for the complete peptonization or liquefaction of the casein, since we know that the gas bacillus does not bring about this change. The study of these samples of 85° C. milk indicates that the spores of aerobes and of the gas bacillus are widely distributed in milk of this vicinity and even suggests that we may be dealing with peculiarly heavy infections of the cow stables or of the dairies with germs of this character. Other anaerobes are also undoubtedly present, but our attention was paid chiefly to the gas bacillus, the presence of which may be regarded as universal.

Milk heated to 85° C. for 30 to 35 minutes and kept at room temperature, about 22° C., shows reactions which are slightly different from the reactions seen in 85° C. samples kept at the body temperature. The variations seem to relate to the time at which the changes manifest themselves and not to any qualitative difference in the reaction. Thus in a number of samples kept at room temperature a firm coagulation occurred within 48 to 72 hours. The coagulum was at times permeated with gas bubbles and the appearance was quite like that described above as violently explosive. At other times the evolution of gas was either lacking or so slight as not to be noticeable, the gas bubbles escaping quietly as they were formed. Peptonization of the clot occurred also in all instances. This peptonization was quite slow, requiring 10 to 14 days for its completion, but the end-result was the same in all cases, a complete liquefaction of the casein.

The changes seen in 85° C. milk kept at room temperature are dependent upon the same organisms as are found in 85° C. milk kept at 37° C. Aerobic cultures revealed the usual spore-bearing bacteria and the gas bacillus was isolated in about half the samples first examined. These examinations were made with specimens which had been kept some time, 10-14 days. In a later series examined for the gas bacillus in the first two days positive isolations resulted in all instances.

Milk heated to 85° C. and then kept on ice at a temperature a few degrees above freezing point undergoes no changes visible to the naked eye. Nevertheless the spores of the organisms originally present retain their vitality for some time and when the samples are placed at a higher temperature, 22-37° C., the various species multiply and bring out the characteristic reactions. A number of samples of 85° C. milk kept on ice for 4-6 weeks revealed no changes, and yet when they were incubated in the thermostat they underwent the decomposition characteristic of 85° C. milk.

Finally the length of time during which milk must be exposed to a temperature of 85° C. to bring out the explosive reaction is by no means always 30-35 minutes. An exposure

for 10 minutes and for 5 minutes also suffices to destroy the non-sporulating organisms and permit the development of the aerobic and anaerobic spore-bearers. Thus in a series of six samples, in which a positive reaction was obtained at 85° C. in all cases, the same reaction was observed in the samples heated to 85° C. for 10 minutes and for 5 minutes.

Milk heated to 80° C. does not differ essentially from that heated to 85° C. and no particular study was conducted on the effects of this temperature. In a series of six samples, in which the characteristic reaction was obtained in all instances at 85° C., the same reaction was observed in samples heated to 80° C. for 30 minutes and also for 20 minutes. No especial attempt was made to find the exact temperature at which the foul, stinking reaction produced by Bienstock's *Bacillus putrificus* occurs in Baltimore milk. This probably lies between 70° and 80° C.¹

REACTIONS OF BOILED MILK.

Milk boiled for 30-35 minutes and then incubated at 37° C. exhibits a variety of changes which may also be seen in the samples preserved at 22° C. In general, three reactions may be noted: clotting without subsequent peptonization; clotting followed by peptonization; and peptonization without clotting. The most frequent reaction in Baltimore milk is the second. Thus in a series of 24 samples, 11 showed clotting, followed by peptonization; 7 showed firm clotting without peptonization, and 6 rapid peptonization without clotting. The explosive reaction seen in 85° C. milk is usually lacking. In the above series it occurred but twice in the 11 samples, showing clotting followed by peptonization. Samples of all these milks heated to 85° C. for 35 minutes showed an explosive reaction and *Bacillus arogenes capsulatus* was isolated from them.

From this series it may be seen that clotting of boiled milk is a more frequent occurrence in Baltimore than the slow peptonization without clotting described by Flügge, since 18 samples in a series of 24 underwent this change. The changes which take place in boiled milk are naturally very slow and the temperature of 100° C. must destroy the vast majority of the microorganisms originally present in the milk. Even when kept at 37° C. the flasks frequently did not reveal any gross changes or abundant bacterial growths for a number of days, while in the samples kept at 22° C. gross changes were

not apparent sometimes for two or three weeks. All our samples of milk boiled 30-35 minutes eventually revealed definite changes due to bacterial development, showing that boiling does not suffice under ordinary circumstances to destroy the bacterial spores present in milk. Our observations are thus in strict agreement with Flügge on this point.

Aerobic cultures from boiled milk revealed nothing but spore-bearing organisms of the "subtilis" and "mesentericus" types, together with our spore-bearing coagulator which is evidently the species usually responsible for the clotting of boiled milk in this vicinity. The gas bacillus is generally absent from boiled milk, its spores evidently not resisting the temperature of 100° C. It was found in two instances only in a series of 12 samples tested for it, these two being the milk which have already been referred to as exhibiting an explosive reaction. Rabbits inoculated with these milks showed the characteristic oedema and the smears and cultures were positive. In the other ten rabbits there was no reaction in the blood or in the organs and the smears and cultures were negative. Since the same samples of milk heated to 85° C. underwent an explosive reaction and the gas bacillus was isolated from them, it was evident that the spores of this species survive boiling only in rare instances, possibly in samples of milk richly seeded with them.

Boiling for shorter periods of time does not affect the milk essentially differently from the exposure for 30-35 minutes. Thus in a series of samples boiled 20 minutes, six samples showed a clot without peptonization, four samples a clot followed by peptonization and two samples a peptonization without clotting. In the same milks boiled 10 minutes the changes were practically identical, except that in one instance an explosive reaction developed, followed by peptonization.

Finally, it may be noted that the complete destruction of bacteria in milk probably occurs only when the milk is boiled for long periods of time or steamed under pressure. Flügge has found that the spores of several species resist boiling for six hours. The application of steam under pressure quickly suffices to kill off all the microorganisms. Thus in six samples of milk which showed an explosive reaction at 85° C., autoclaving with a pressure of 20 lbs. for 5, 10 and 15 minutes gave samples of milk which could be kept for months without revealing any changes attributable to bacterial development.

The reactions seen in milk heated to various temperatures may best be illustrated by the following table which gives the results of our final series of experiments. Here it may be noted that the raw milk clotted normally and showed the gas bacillus in two instances only; 65° C. milk showed an explosive reaction in all instances and yet failed to reveal the gas bacillus; 85° C. milk showed an explosive reaction in all instances, both at 37° C. and at 22° C., and revealed the gas bacillus in all cases in which rabbit inoculations were made; boiled milk showed an explosive reaction with positive gas bacillus isolation in two instances, clotted without peptonization in three instances and peptonized without clotting in one instance, the last four being negative for the gas bacillus.

¹ Similar reactions to those described above have been observed by Klein¹⁴ in London milk and have been attributed by him to an organism which he called *Bacillus enteritides sporogenes* and which he regarded as an etiological factor in summer diarrhoea. The reactions originally published by Klein cannot be reconciled with those of a pure culture and in subsequent publications the reactions attributed to pure cultures of *Bacillus enteritides sporogenes* correspond closely to those given by Welch and Nuttall for *Bacillus arogenes capsulatus*. The proof that Klein's organism is a distinct species cannot in our opinion be regarded as satisfactory. In addition, it may be noted that cultures of *Bacillus enteritides sporogenes* sent to this laboratory some years ago revealed *Bacillus arogenes capsulatus* mixed with an aërobe.

W. W. FORD.

SIX SPECIMENS BALTIMORE MARKET MILK TESTED MAY 31, 1913.

No.	I.	Treatment	Preserved at	Reaction	Gas Bacillus
		65° C.—35 min.	37° C.	Explosive	Negative
		85° "—35 min.	37° "	Explosive
		85° "—35 min.	22° "	Explosive	Positive
		100° "—35 min.	37° "	Clotted	Negative
		Raw control	37° "	Clotted	Negative
No. II.		65° C.—35 min.	37° C.	Explosive	Negative
		85° "—35 min.	37° "	Explosive
		85° "—35 min.	22° "	Explosive	Positive
		100° "—35 min.	37° "	Clotted	Negative
		Raw control	37° "	Clotted	Positive
No. III.		65° C.—35 min.	37° C.	Explosive	Negative
		85° "—35 min.	37° "	Explosive
		85° "—35 min.	22° "	Explosive	Positive
		100° "—35 min.	37° "	Explosive	Positive
		Raw control	37° "	Clotted	Negative
No. IV.		65° C.—35 min.	37° C.	Explosive	Negative
		85° "—35 min.	37° "	Explosive
		85° "—35 min.	22° "	Explosive	Positive
		100° "—35 min.	37° "	Clotted	Negative
		Raw control	37° "	Clotted	Negative
No. V.		65° C.—35 min.	37° C.	Explosive	Negative
		85° "—35 min.	37° "	Explosive
		85° "—35 min.	22° "	Explosive	Positive
		100° "—35 min.	37° "	Peptonized	Negative
		Raw control	37° "	Clotted	Positive
No. VI.		65° C.—35 min.	37° C.	Explosive	Negative
		85° "—35 min.	37° "	Explosive
		85° "—35 min.	22° "	Explosive	Positive
		100° "—35 min.	37° "	Explosive	Positive
		Raw control	37° "	Clotted	Negative

GENERAL CONSIDERATIONS.

From these experiments upon the effect of heat of various degrees upon milk, this effect being determined by a study of the ultimate changes which the milk undergoes, it is evident that most important biological laws involving the relationship of bacteria are involved. Under ordinary circumstances there are bacteria of three general groups in milk, the aerobic non-sporulating organisms, of which the most abundant are the lactic acid bacteria, the aerobic spore-bearing organisms and the anaerobes. These are also in most cases spore-bearing. In raw milk the bacteria of the first group, the lactic acid producers, predominate, and as the milk gets old it sours and clots, due to their multiplication. This may be regarded as the most desirable change in milk, since it resembles most closely the changes which take place in the human intestine while the bacteria involved are entirely free from pathogenicity and may even be beneficial when taken into the alimentary canal. The lactic acid organisms moreover, by their multiplication, may almost completely inhibit the aerobic and anaerobic spore-bearing organisms present in the milk. Furthermore, raw milk has its own danger signal, since the acid produced as it sours, while harmless, is rather disagreeable in taste, and thus prevents the use of an old milk which might contain harmful ingredients. As milk is heated the various groups

of bacteria are affected in different ways. Beginning at 60° C. we have normally a destruction of the lactic acid bacteria. These may not all succumb at this temperature, but the balance of bacterial growth is altered so that spore-bearing organisms begin to develop and gaseous putrefactive changes begin to occur. How frequent a normal clotting is in Baltimore milk heated to 60° C. is not clear, nor have we determined definitely the relation of this clotting at 60° C. to the original character of the milk nor to the method of keeping it. In the majority of instances in the experiments thus far conducted normal clotting is somewhat rare in 60° C. milk and the clotting which does occur is followed by peptonization. Frequently the reaction is explosive in character. In milk heated to 65° C. there is a further destruction of the lactic acid bacteria; the sporulating organisms are more predominant and the changes which the milk undergoes are nearly always explosive and peptonizing. This reaction is not due to the gas bacillus, but probably to other anaerobes. As the temperature to which milk is subjected is raised to 85° C. the lactic acid organisms are entirely destroyed, and the gas bacillus (with other anaerobes) develops, giving rise to an explosive reaction with butyric acid as one of the main products. At the same time the aerobic spore-bearing organisms appear in great profusion and variety, converting the curd produced by the gas bacillus or other organisms into a thin, slimy liquid with eventually the disagreeable odor of putrefaction. This change must be regarded as the most undesirable change in milk, since by it the milk is rendered unpalatable and its food value probably destroyed. It must also be remembered that milk heated to 85° C. will explode and decompose even when kept at room temperature, and that the spores which bring about this change survive for a long time on ice. Furthermore an exposure of milk to 85° C. for only 10 minutes suffices to bring about this change in the character of the organisms present in the milk. As the temperature to which milk is heated is still further raised to 100° C. the bacteria which give rise to the explosive putrefactive reaction are destroyed in a short space of time and a new set of reactions is seen in the milk. Boiled milk rarely explodes, but either elots or slowly peptonizes. Finally the complete destruction of the bacterial spores in milk is only accomplished by subjecting the milk to the action of steam under pressure. All these reactions should be kept clearly in mind when working out the scientific principles of milk pasteurization. It may be possible to determine just what the underlying factors are which permit a clotting of milk heated to 60-65° C. and on this devise methods for the pasteurization of milk which will not do away with its capacity of normal coagulation. Heating milk to temperatures above 65° C. in the hope of surely exterminating pathogenic bacteria is of itself a dangerous procedure, since the milk is thus converted into a material in which bacterial development with the production of noxious products is almost certain to occur with the lapse of time. If milk must be heated to over 65° C. to destroy infectious material it should be boiled, since in that way the danger zone of milk heating, ranging from 65° to 85° C.,

may surely be avoided. Finally if such a beautiful antagonism exists in milk between the lactic acid organisms and the spore-bearing aerobes and anaerobes, a similar antagonism may exist also in the intestinal tract of man. If this be so, the use of cultures of lactic acid bacteria in intestinal derangements due to the growth of spore-bearers would be advisable while the employment of milk in which the lactic acid organisms are destroyed would be contra-indicated.

From the various experiments reported in this paper we feel justified in drawing the following conclusions:

CONCLUSIONS.

1. As first pointed out by Flügge, milk always contains the heat-resistant spores of aerobic and anaerobic bacteria, which, by their development, can give rise to disagreeable and unwholesome changes in milk, converting it from a food of great nutritive value into an undesirable if not a dangerous article of diet.

2. These changes take place in milk heated to any temperature from 65° C. to 100° C. and kept at any temperature from 22° C. to 37° C., but not at that of the ice box, 4°-6° C.

3. The spores of the bacteria causing these changes survive in milk for long periods of time on ice and can initiate the same changes in milk kept on ice when transferred to higher temperatures.

4. There is a danger zone in the heating of milk which may be described as ranging from about 65° C. to 85° C. in which milk will never clot normally. Below this temperature heated milk may clot normally. Above this temperature milk will either clot or slowly peptonize.

5. The problem of pasteurization of milk must be worked out on the basis of the changes which occur in milk heated to 60°-65° C. and the result may depend upon the original character of the milk, upon local bacterial infections of milk, on the character of the stables in which the milk is first obtained, upon methods of preservation or upon unknown factors. Further investigation alone can determine these points.

6. With our present knowledge as to the difficulty of getting milk free from pathogenic organisms the safest milk is that which has been boiled for a time varying from ten minutes to half an hour and then preserved on ice. In such milk the organisms giving rise to explosive and putrefactive changes are destroyed, while the organisms which remain usually coagulate the milk or coagulate it and then peptonize it. Rarely they peptonize it without coagulation. While these bacteria may give rise to severe derangements of metabolism in children, and even to disease, as Flügge maintains, this has not yet been clearly shown clinically. Danger from them may probably be almost entirely eliminated by keeping the milk on ice from the time of boiling till the time of use.

7. Milk heated to any temperature from 60° C. to 100° C. must be kept on ice, since heated milk is far more apt to decompose than raw milk.

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ON THE PRESENCE OF SPORE-BEARING BACTERIA IN WASHINGTON MARKET MILK.¹

By JAMES C. PRYOR, M. D.

(From the Laboratory of Hygiene and Bacteriology, Johns Hopkins University, Baltimore, and the Naval Medical School, Washington.)

Washington market milk at the present time is sold under fairly strict sanitary supervision, owing chiefly to the extensive campaign in that city against typhoid fever, during the course of which it was shown that this disease could be traced in many instances to a contaminated milk supply. In consequence, the conditions under which the milk is handled in Washington have been greatly improved during the past few

years. The sale of dipped milk, while permitted, has almost ceased. Most of the milk is bottled and is usually preserved in the retail establishments on ice. Much of the bottled milk is pasteurized at a temperature of 60°-65° C. for 25 to 30 minutes. During the course of this study 51 samples of market milk were examined, 24 of which were raw milk from 17 different dairies, while 27 were commercially pasteurized milk from 8 different sources. A number of samples of the better grades of milk, such as that coming from the Walker-Gordon farms, were also included in this series, so that prac-

¹Being the synopsis of a thesis submitted to the Board of University Studies, Johns Hopkins University, for the degree of Master of Arts.

tically every variety of milk was represented. The results obtained do not differ materially from those found by Ford and Pryor in their study of Baltimore milk and show that the conclusions reached by those authors apply to Washington as well as to Baltimore. Thus in 30 consecutive samples of milk heated to, and held at, 85° C. for 30-35 minutes, and incubated at 37° C., an explosive reaction with gas evolution occurred almost without exception and a complete liquefaction of the proteids in the milk was observed in every instance. In 27 of these 30 samples the *Bacillus arogenes capsulatus* of Welch and Nuttall (gas bacillus) was obtained by rabbit inoculation of one cubic centimeter quantities by the classical method, the animals showing the usual reactions in the blood and in the various organs, particularly the liver, characteristic organisms being cultivated from the blood stream. In the three negative instances the characteristic reaction was lacking from the liver and the organism was not obtained on cultures, but bacteria resembling the gas bacillus were observed in smears from the tissues in one case. It is evident therefore that this organism is practically a constant inhabitant of the milk in Washington (27 out of 30 cases = 90 per cent) and can be demonstrated if proper methods be employed. This series of 30 samples includes both raw and commercially pasteurized milk. Controls of unheated milk placed in the thermostat at 37° C. showed in all instances a normal coagulation. Specimens of the same milk to the number of 26 heated to 85° C. and then kept on ice at a temperature of two to three degrees above the freezing point showed no gross changes in periods of time varying from two weeks to two months, but in all instances when transferred to the thermostat at a temperature of 37° C. underwent the same changes as the original 85° C. samples; namely, coagulation, gas production and complete liquefaction. The spores of the organisms giving rise to this reaction are thus capable of surviving long periods of time at low temperatures and give rise to the characteristic changes when placed at a temperature suitable for their development.

Another series of samples of Washington milk was examined for the presence of aerobic spore-bearers. This series included twelve samples of commercially pasteurized milk and nine samples of raw milk. Each specimen was divided into four parts, one heated to 65° C., one to 85° C., one boiled, one preserved as an unheated control. After incubation at 22° C. to 37° C. for periods of time varying from 48 to 72 hours in order to insure a full development of the bacteria present in milk, plates were poured and various colonies picked up and identified. All the raw controls clotted normally and cultures showed the usual lactic acid bacteria with but few sporulating organisms. Of the samples heated to 65° C. but one specimen showed a normal clot. Eleven samples exhibited an explosive reaction with coagulation and gas evolution followed by peptonization, while nine specimens underwent coagulation followed by a peptonization. Aerobic cultures taken from these specimens showed only spore-bearing organisms, except in the

one sample which clotted normally and in which lactic acid organisms developed on the plates. These spore-bearers belonged in general to the group of peptonizing gelatin liquefiers, but a number of cultures of the organism mentioned in the previous paper of Ford and Pryor, which acidify and coagulate milk, were also obtained. It would seem therefore that a normal clotting of Washington market milk heated to 65° C. is extremely rare and that this temperature applied for 30-35 minutes under laboratory conditions suffices to destroy the lactic acid bacteria normally present or at least so to inhibit them or reduce their numbers as to permit an abundant development of spore-bearing organisms. Furthermore, a clotting of 65° C. milk does not of itself indicate the survival of the true lactic acid organisms, since there are definite species of spore-bearing bacteria which have the property of fermenting lactose to an acid reaction and acidifying and coagulating milk. How far this conclusion holds true for commercially pasteurized milk is not clear. The various specimens of Washington market milk labeled "pasteurized" which we have had the opportunity of studying clotted normally when preserved at 37° C. or at 22° C. and did not differ in any particular from ordinary raw milk. Plates poured from this commercially "pasteurized" milk furthermore revealed only the lactic acid bacteria characteristic of raw milk. A serious question is raised therefore as to what significance the term "pasteurization" has in regard to Washington milk and to what temperature such milk actually has been raised.

The samples of milk heated to 85° C. showed an explosive reaction with peptonization in 12 instances, in 9 cases a clot being produced followed by a peptonization. Cultures made from these samples revealed only spore-bearing species of much the same general type as those found in 65° C. milk, but no lactic acid bacteria were found on the plates. Several representatives of the acid-producing milk-coagulating spore-bearer previously mentioned were encountered, together with the peptonizing species usually present in 65° C. milk.

Finally the specimens of boiled milk showed an explosive reaction in a much larger proportion of cases than did the Baltimore samples, this reaction being found in 7 cases out of 21. The other samples clotted and slowly peptonized, except in one instance, where the boiled milk suffered no change. Plates poured from all the specimens which showed gross reactions revealed an abundant growth of spore-bearing species which belonged in general to these groups: first, organisms which liquefy gelatin and produce no special changes in litmus milk; second, organisms which liquefy gelatin and peptonize litmus milk with an alkaline reaction; third, organisms which liquefy gelatin, acidify and clot litmus milk and then very slowly dissolve the coagulum.

From this series of 21 samples it is evident therefore that aerobic spore-bearing organisms are widely distributed in Washington market milk and that it is practically impossible to find specimens which do not reveal them when proper methods for their isolation are applied.

CONCLUSION.

From the study of over fifty samples of Washington market milk representing fairly accurately the different kinds of milk sold in the city, we are able to confirm Flügge's original observation as to the presence of spore-bearing bacteria. In our experience the most important anaerobic species is *Bacillus ærogenes capsulatus*, which we believe to be universally present. Aerobic spore-bearing bacteria are also found in practically all samples, such organisms belonging in general to the

group of gelatin liquefiers. Such species do not develop normally in raw milk nor in the milk sold in Washington as "pasteurized," only the ordinary lactic acid bacteria being found. All these spore-bearing organisms have a profound effect upon milk and when their development is not hindered by the lactic acid bacteria will produce changes of decomposition and putrefaction, rendering the milk unfit for food. How far they play a rôle in clinical conditions, especially in children, remains to be proved.

THE ACTION OF POTASSIUM AND SODIUM IODIDES AND OF THE IODINE ION ON THE HEART AND BLOOD VESSELS.*

By DAVID I. MACHT, M. D.

(From the Departments of Medicine and Pharmacology, Johns Hopkins University.)

The iodides, and more particularly the iodides of potassium and sodium, occupy an important place in all pharmacopœias. They have been advocated on purely empirical grounds, in a great many conditions. Their administration in the later stages of lues, in imperfectly understood rheumatic and neuralgic conditions, in various forms of asthma, bronchitis, cirrhosis, and in almost every form of obscure disease is familiar to all.

The rationale and the scientific basis of this usage, however, are very inadequate, and more exact knowledge of the action of these drugs is very much needed.

Among the commonest indications for the use of the iodides are said to be certain cardio-vascular conditions, namely, aneurism and arteriosclerosis. What their action is in such cases is not very clear. According to some¹ they are supposed to promote absorption and to prevent the formation of connective tissue, though this has never been proven. According to others² the circulation is improved chiefly through a decrease in the viscosity of the blood produced by the drugs.

Still others³ ascribe to the iodides a lowering of the blood pressure. Thus Huchard attributes to the iodides the power "to lower arterial tension, to render more active the nutrition of organs, to effect resolution of degenerative processes in the vessel walls, and to lower peripheral resistance."⁴

This effect of the iodides on the blood pressure attracted the attention of numerous observers, mostly clinicians, but there is still no unanimity of opinion on the subject. Potain⁵ was one of the first to extol this virtue of the iodides in lowering the blood pressure, which he thought was brought about by their action on the heart and vasomotor nerves. Chelmonski⁶ is so sanguine as to the pressure-lowering effect of the iodides that he urges their use in internal hemorrhage, and recently Lucibelli⁷ advocated their use in hypertension. On the other hand, other clinicians, as Romberg,⁸ Kraus,⁹ and Mackenzie,¹⁰ do not note any influence on the arterial lumen or on the heart.

In animal experiments the findings of different observers

are also widely different. Sée and Lapique¹¹ noted after intravenous injections of potassium iodide first a rise and then a fall of blood pressure, which they oddly enough explain by saying that potassium stimulates the heart in a manner comparable to digitalis, and iodine causes a dilatation of the vessels. Huchard and Eloy¹² obtained a marked fall in blood pressure from administration of potassium iodide to rabbits, but only after large doses. Prévost and Binet¹³ failed to obtain any effect on arterial pressure from moderate doses, while excessive doses produced a fatal fall. Barbera¹⁴ reported a slowing of the pulse and fall of blood pressure in animals after large doses of sodium iodide, which he attributed to a paralysis of the depressor nerves of the heart. Gumprecht¹⁵ in a large series of experiments on rabbits concluded that small and large doses of iodides were without influence on the pressure; that only extremely large doses endangering life cause a fall in tension; and that neither a local action on the vessel wall nor a paralysis of the vasomotor center could be demonstrated. Finally, Stockman and Charteris¹⁶ state that after administering the iodides to patients in doses of from 15 to 40 grs. per day for many days, and in all kinds of normal and pathological cases, they noted no effect on the blood pressure. In animal experiments, according to these authors, when administering NaI or KI by mouth no effect was observed; after intravenous injections, however, while NaI had no effect, KI caused depression of the heart, which was sometimes fatal.

On reviewing the work of the above observers, it would seem that their aim was primarily to ascertain the action of the iodides as such, no special attention being paid to the relative pharmacodynamic rôles played by their constituent parts, namely, by the iodine and the potassium or sodium. The present research was accordingly undertaken especially with a view of determining just how the constituent elements of the salts KI and NaI act on the heart and blood vessels, individually and in combination with each other.

It is perhaps also well to state definitely here at the beginning of the paper, that though the action of potassium, sodium, and iodine in this research is often referred to as an "ion" action, such expressions as potassium ions, sodium ions

*Paper read at a meeting of The Johns Hopkins Hospital Medical Society, May 18, 1914.

and iodine ions are employed more for convenience of description in accordance with the common usage of recent writers, rather than as an attempt to explain exactly how those elements produce their effect on the individual living cells. All that we do know is that K, Na, and I ions are present in the solutions used; but whether those ions act directly as such or indirectly through some intermediary physical or chemical process is left an open question. Indeed there are authors who are inclined to the view that the iodine action is a molecular action,¹⁷ and the fact that in our experiments, as will be seen later, elementary iodine in solution acted in a manner similar to the other iodine effects described in this paper, would tend to lend support to this view.

METHOD.

A normal Locke's solution was made, and then modifications of it were prepared containing the substance, the action of which it was desired to test. These solutions were used in perfusing the blood vessels of cold and warm blooded animals, in perfusing amphibian and mammalian hearts, in studying the behavior of excised arterial rings and strips and in blood pressure experiments. In all cases controls with normal Locke's solution were made.

Normal Locke's solution was prepared according to the following formula:

CaCl ₂	0.024 per cent (crystals)
KCl	0.042 per cent
NaHCO ₃	0.030 per cent
NaCl	0.900 per cent
Dextrose	0.100 per cent

For convenience of preparing this solution three stock solutions were made as follows:

Solution A.	Solution B.	Solution C.
NaHCO ₃ 3.0 gm.	NaCl 90 gm.	CaCl ₂ 2.4 gm
KCl 4.2 gm.	Water 1000 cc.	Water 100 cc.
Water 100 cc.		

To make one liter of Locke's solution 10 cc. of A, 100 cc. of B, and 10 cc. of C are mixed with 900 cc. of water and 1 gm. of dextrose is dissolved in the mixture. In order to study the action of the potassium, part of the NaCl in normal Locke was replaced by its *equimolecular* weight of KCl. Thus, for instance, by substituting 2.6 gm. of KCl in place of 2 gm. of NaCl in a liter of normal Locke solution, a solution differing from normal Locke solution only in containing a larger number of K ions, is obtained. By substituting 4 gm. of NaCl by 5.2 gm. of KCl, another solution of greater C_K (concentration of K ions) is obtained.

In order to get at the action of the iodine ion, substitutions of the normal KCl in part or wholly by its equimolecular quantity of KI were made. To obtain a still greater C_I (concentration of I ions) part of the normal NaCl instead of the KCl was replaced by its physico-chemical equivalent of NaI.

In a similar manner other substituted Locke's solutions were made.

I have also experimented with solutions of elementary iodine

in normal Locke solution; and various other solutions to be described later.

EXPERIMENTS IN PERFUSION OF BLOOD VESSELS.

The vessels of the hindlegs of a frog were prepared by a modification of the Laewen-Trendelenburg method. The inflow cannula was inserted in the abdominal aorta above its bifurcation, the perfusion fluid being injected at a pressure of 35 cm. and the drop outflow from the veins of the legs being registered automatically on a revolving drum. The results of the experiments were as follows:

The iodine ion markedly increases the vascular tone or constricts the frog's vessels.

The potassium ion causes a relaxation or dilatation of the frog's vessels.

The sodium ion has very little or no effect, and if anything, *increases* the vascular tone.

The effect of injections of the salts KI and NaI is a combination of the effects of their component ions. Sodium iodide causes distinct constriction or increase in the vascular tonus of the frog's vessels. Potassium iodide produces either no effect or a very slight increase in tone, thus indicating that the iodine effect balances and even over-balances the action of the potassium ions. It is well to mention that this depressing effect of potassium on the vessels of a frog has been shown previously, though not on strictly physico-chemical lines, by Hooker.¹⁸ That author studied the effect of Ringer's solution as compared with that solution minus the *whole potassium salt*. For the sake of comparison I have also perfused the vessels with a weak solution of *elementary iodine*, and with a weak solution of hydriodic acid. The elementary iodine in weak solution (1 to 14000), also produces a contraction of the vessels. Hydriodic acid paralyzes the vessel walls (hydrogen ion) and causes a marked increase in outflow.

Having studied the action of the K, Na, and I ions on the frog's vessel walls, it was desirable to ascertain their action on the vessels of a warm-blooded animal, for although the action of drugs on the vessels of a mammal is generally the same as on those of the frog, still it is not always the same. Gunn,¹⁹ for instance, has shown that some substances, namely, quinine, yohimbine, and apocodeine, while acting as vaso-dilators on higher animals, bring about a constriction of the frog's blood vessels. I have, therefore, tested the effect of my solutions on the mammalian blood-vessels, by the ingenious method employed by the Russian investigator, Pissemiski,²⁰ namely, that of perfusing a rabbit's ear.*

This interesting method was employed by us previously in another research.²¹ It is simple, though requiring some practice. A needle or cannula is inserted in the central artery of an amputated rabbit's ear, and oxygenated fluid is perfused through it, the outflow from the veins being recorded as in the case of a frog. At a constant room temperature the normal

* In all the experiments on animals, great care was taken to have them completely anæsthetized before performing any operation.

outflow is very constant, and if the perfusing fluid is left at the same temperature the results are quite reliable.

Perfusion of a rabbit's ear gave the same results as in the case of a frog. Iodine ions caused marked constriction, while potassium ions produced dilatation of the vessels.

The findings mentioned above are illustrated by the following protocols and tracings:

EXPERIMENT I.

PERFUSION OF FROG'S HIND LEGS.

Normal Locke Solution.	Outflow 9 drops per 30 secs.
Inject 10 mg. KI.	
1 minute later	" 8 " " " "
3 " "	" 7 " " " "
5 " "	" 7 " " " "
10 " "	" 8 " " " "
15 " "	" 8 " " " "
30 " "	" 8 " " " "

EXPERIMENT II.

PERFUSION OF FROG'S HIND LEGS.

Normal Locke Solution.	Outflow 8 drops per 30 secs.
Inject KI 10 mg.	
1 minute later	" 7 " " " "
3 " "	" 7 " " " "
5 " "	" 7 " " " "
10 " "	" 6 " " " "
15 " "	" 7 " " " "
30 " "	" 7 " " " "

EXPERIMENT III.

PERFUSION OF FROG'S HIND LEGS.

Normal Locke Solution.	Outflow 14 drops per 30 secs.
Inject 10 mg. NaI.	
30 seconds later	" 14 " " " "
1 minute "	" 10 " " " "
2 " "	" 8 " " " "
3 " "	" 8 " " " "
5 " "	" 8 " " " "
10 " "	" 9 " " " "
15 " "	" 10 " " " "
30 " "	" 12 " " " "

EXPERIMENT IV.

PERFUSION OF FROG'S HIND LEGS.

Normal Locke Solution.	Outflow 7 drops per 30 secs.
Inject 1 cc. of elementary iodine in normal Locke (1 to 14000).	
2 minutes later	Outflow 5 drops per 30 secs.
5 " "	" 4 " " " "
10 " "	" 4 " " " "
15 " "	" 4 " " " "
20 " "	" 4 " " " "
30 " "	" 5 " " " "

EXPERIMENT V.

PERFUSION OF FROG'S HIND LEGS.

Normal Locke Solution.	Outflow 7 drops per 30 secs.
Inject 1 cc. HI dil. (0.1%).	
1 minute later	" 8 " " " "
2 " "	" 10 " " " "
5 " "	" 11 " " " "
10 " "	" 11 " " " "
15 " "	" 15 " " " "
30 " "	" 15 " " " "

See figs. 1 and 2.



FIG. 1.—Perfusion of rabbit's ear.

A.—Normal Locke; 10 drops in 30 secs.

B.—"K ion" Locke; 13 drops in 30 secs.

C.—"I ion" Locke; 8 drops in 30 secs.

B = Locke with 2 gm. of NaCl replaced by 2.6 gm. KCl per liter.

C = Locke with 2 gm. of KCl replaced by 4.4 gm. KI per liter.



FIG. 2.—Perfusion of frog's vessels, showing effect of iodine ions.

A.—Normal Locke.

B.—5 min. after injection of iodine ions.

C.—10 min. later.

ACTION ON ARTERIAL STRIPS.

The action on arterial rings or strips was studied according to a modification of the original method of O. B. Meyer,²² and is the same as was used by Dr. Voegtlin and myself²³ on the coronary artery and in my work on the pulmonary.²⁴ Rings or strips of the carotid, the coronary, the external iliae, and the pulmonary arteries of the ox and the pig were employed. These were suspended first in normal oxygenated Locke's solution at 37° C., and then the normal Locke solution was replaced by the modified solutions already described. It was found by this method also that the potassium ion causes a relaxation of the vessels, and the iodine ion a marked constriction. The action of KI as such is a combination of these two effects, but whereas in the case of perfusion of the frog's vessels, the iodine effect seems to predominate and there is a slight tendency to a diminution of outflow, that is, to increased tonicity, in case of the warm-blooded animals the vessels seem to be more sensitive to the potassium ions and there is a tendency to depression of tone or relaxation. This is especially true of the coronary

arteries, where marked relaxation was noted. On the pulmonary artery potassium iodide showed no effect (Figs. 3 and 4).

ACTION ON THE FROG'S AND THE MAMMALIAN HEART.

The effect on the frog's heart is very striking, as may be seen from the illustrations. It was found that the potassium

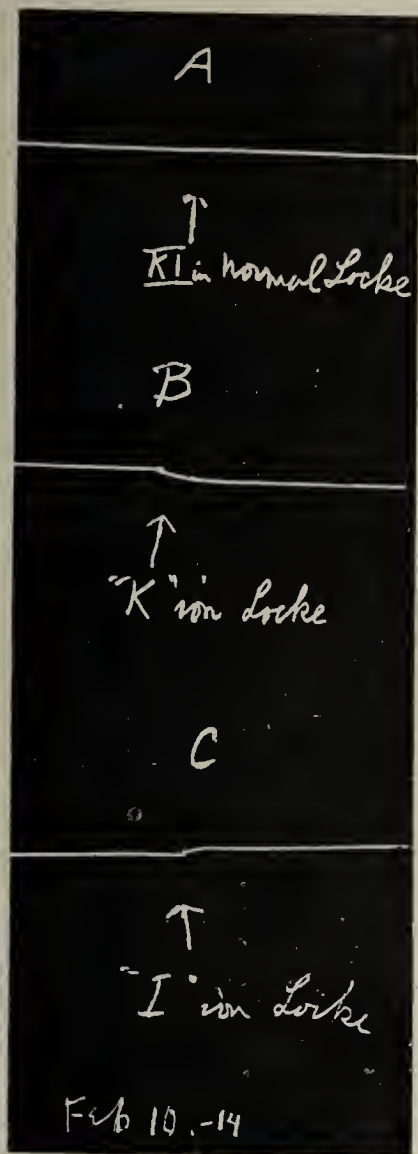


FIG. 3.—Pig's ext. iliac artery; 3 strips, size 10 mm. by 3 mm. each; stretching wt., 30 gm.; lifting wt., 11 gm.

- A.—Effect of 1 per cent sol. KI in normal Locke. No effect.
 B.—Effect of Locke with half of the NaCl substituted by equimolecular quantity of KCl. "K ions" produce relaxation.
 C.—Effect of Locke with half of the NaCl replaced by equimolecular quantity of NaI. "I ions" produce contraction.

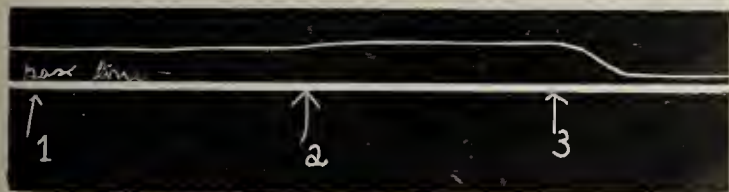


FIG. 4.—Ox coronary, 5 rings; stretching wt., 60 gm.; lifting wt., 40 gm.; speed of drum, 12 hrs.

- 1.—Normal Locke.
 2.—"I ion" Locke = Locke with 2 gm. KCl replaced by 4.4 gm. of KI per liter.
 3.—KI 20 ing. in normal Locke.

ion, as has been well known, has a very depressing action, causing speedy standstill in diastole. The iodine ion on the other hand is an active stimulant. The sodium ion has also a slightly

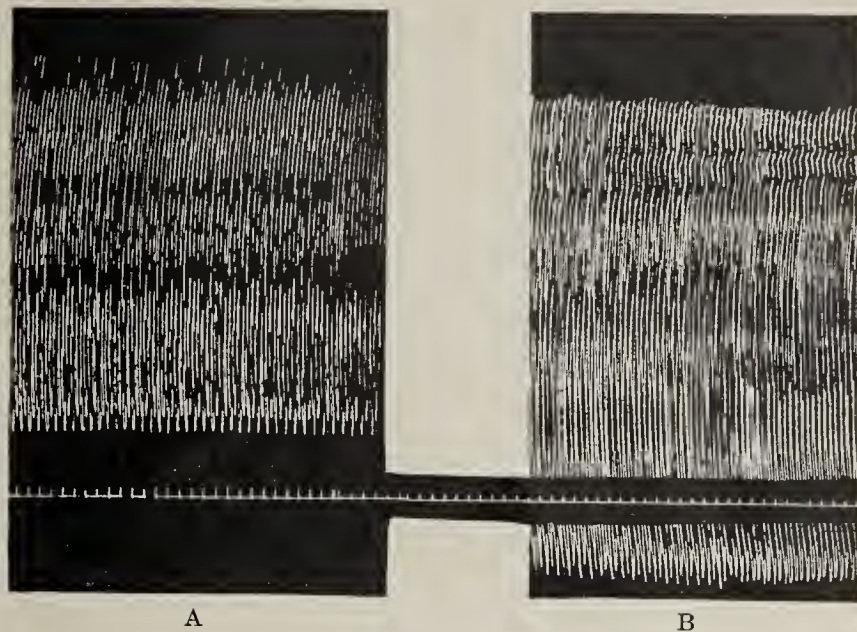


FIG. 6.—Perfusion of cat's heart; Martin's method; showing increase in force of beat and in volume output. Downstroke = systole.

- A.—Normal Locke. Output = 10 cc. in 30 secs.
 B.—Effect of "iodine ions." Locke with KCl replaced by KI. Output = 15 cc. in 30 secs.

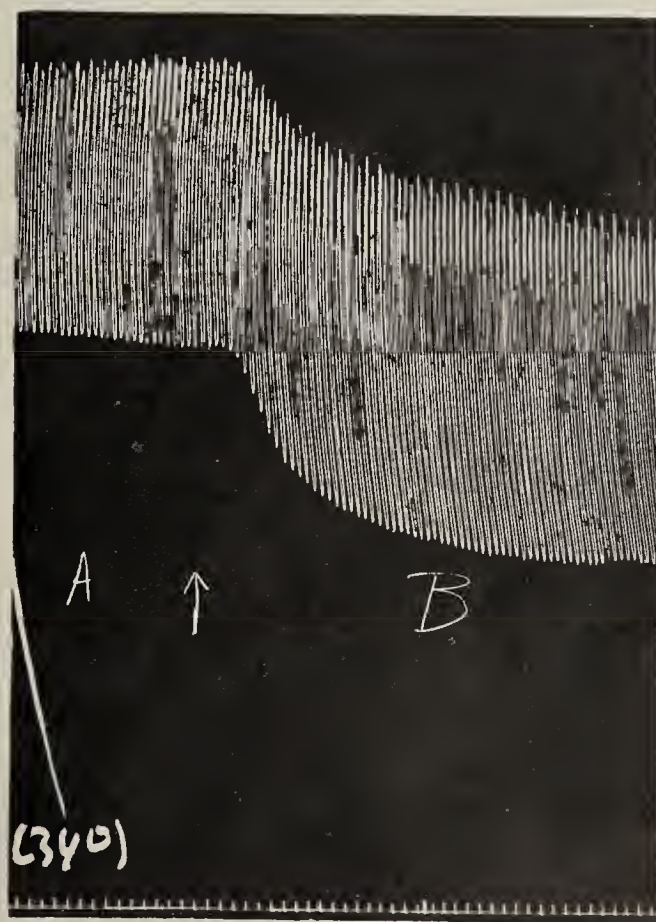


FIG. 7.—A.—Normal Locke. Downstroke-systole.
 B.—Locke with KI in place of KCl.

Cat's heart. Perfusion by Martin's method; showing increase of tonicity and force of beat caused by iodine ions. Downstroke = systole.

tonic effect on the heart. The action of sodium and potassium iodides can be easily explained by bearing in mind the component factors. Sodium iodide containing no depressing fac-

the beat, and stronger solutions arrest the heart altogether (Fig. 5).

In order to corroborate the above findings a series of experi-

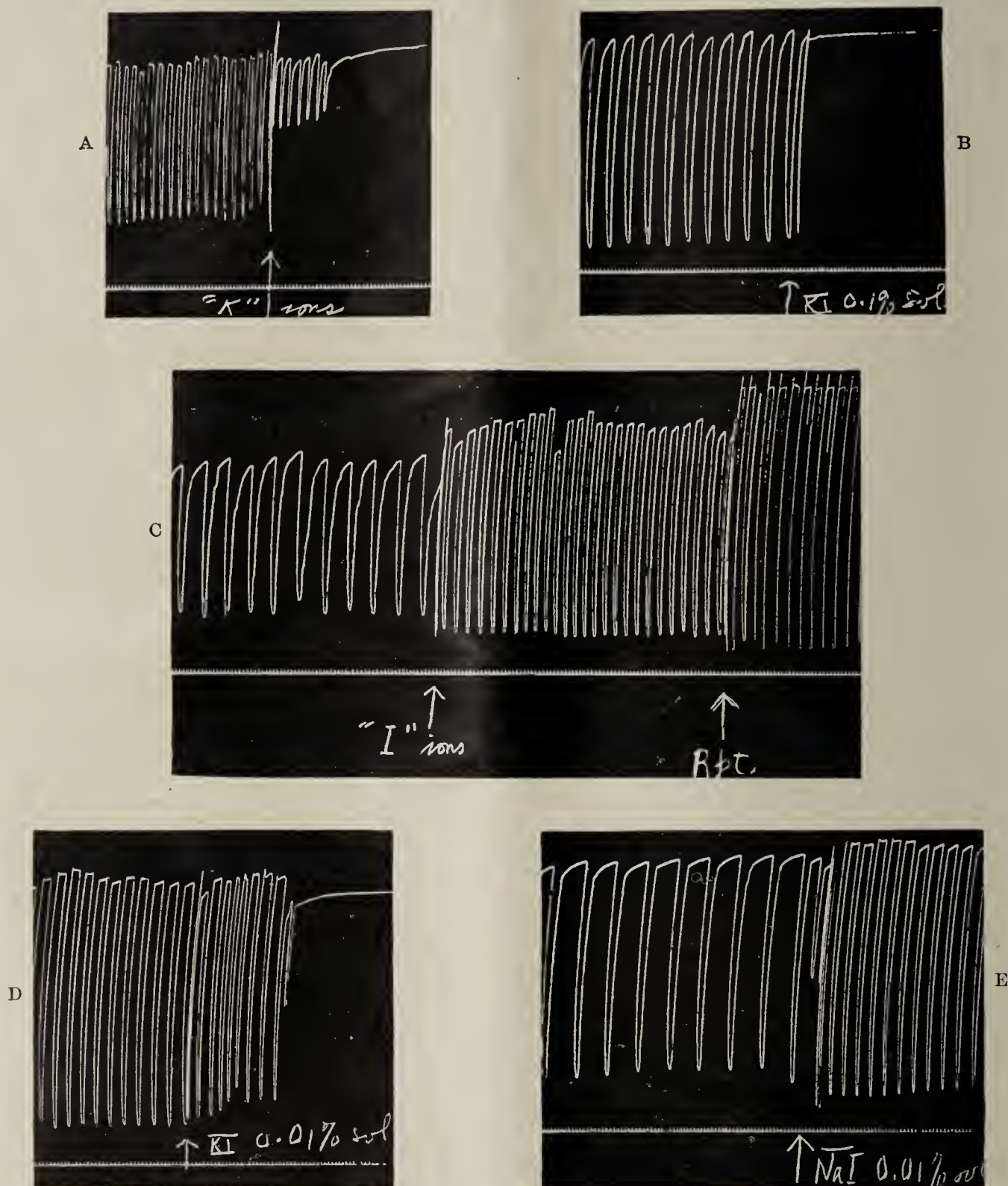


FIG. 5.—Perfusion of frog's heart; suspension method. First part of each tracing is the effect of normal Locke. Arrow indicates introduction of substance tested. Downstroke = systole.

A.—Effect of K ions = Locke with half of NaCl replaced by equimolecular quantity of KCl.

B. and D.—Effect of KI dissolved in normal Locke = combined effect of K and I.

C.—Effect of iodine ions = Locke with half of NaCl replaced by NaI.

E.—Effect of NaI dissolved in normal Locke = combined effect of Na and I.

tor produces stimulation. Potassium iodide on the other hand shows the predominating influence of the potassium ions, so that weak solutions of KI produce a slowing and weakening of

ments were also made with a new Locke's solution, which we may term "acetate" Locke solution. This was prepared exactly like ordinary Locke solution, with the exception of the

sodium bicarbonate. Instead of HNaCO_3 , an equivalent amount of sodium acetate was substituted. Such an acetate solution acts on the heart just as well as and even better than ordinary Locke's solution. Using this acetate solution as a standard, substitutions of it were made to show the effect of K or I ions. Here, too, it was found that potassium depresses, while iodine stimulates, the heart.

Finally, the effect on a mammalian heart was studied by perfusing cats' hearts, by Martin's method. Here again potassium caused depression and iodine stimulation of the heart. Potassium iodide produced depression. The tracings show well the increase in the force of the beat and volume-output, and also the greater tonicity produced by iodine ions (Figs. 6 and 7).

EFFECT ON INTACT ANIMALS.

To complete the study of the action of the iodides as such and of their constituent elements, observations were made on blood pressures in intact animals, and here a very interesting phenomenon was noted.

Normal Locke solution injected in quantities of 5 cc. per kilo weight of animal (dog) produced no appreciable change in blood pressure. Sodium iodide and potassium iodide injected as salts dissolved in normal Locke solution in small doses also showed no effect. Larger doses of sodium iodide, 100 mg. per kilo at a time, produced no effect or a slight tendency to a rise in blood pressure. Potassium iodide, however, in doses of 100 mg. per kilo, produced a marked *fall* in blood pressure. This fall in blood pressure after KI was due to the effect of the potassium ions, for it was found that 5 cc. per kilo of a substituted normal Locke solution, containing 0.50 per cent of KCl, in place of 0.40 per cent of NaCl, injected into a dog's vein produced a fall of from 10 to 20 mm. of mercury.

When, however, we studied the action of an "iodine" Locke solution, that is, the action of iodine ions on the blood pressure, contrary to our expectations no rise in blood pressure could be noted. Thus, for instance, 5 cc per kilo of a substituted normal Locke solution containing 1.04 per cent of NaI in place of 0.40 per cent NaCl injected intravenously into a dog, produced no rise in blood pressure. On repeated injections of the same solution a slight increase in the force of the heart beat was observed, and the pressure rose some 5 to 10 mm., but this effect was of short duration, and was by no means as striking as the powerful vaso-constriction and cardiac stimulation produced by iodine ions on isolated organs.

The explanation of this anomalous action was cleared up in a simple manner.

Many years ago Rudolf Boehm,²⁸ in studying the toxicity of iodine, noted that considerable quantities of iodine could be injected into an animal without untoward results, and in all his experiments he never noted a rise in pressure after such injections.

This detoxification of iodine he showed was due to a chemical combination of iodine with the proteids of the blood. I accordingly suspected that just as elementary iodine combined with proteids, so it was possible that iodine in ionic state, such as we

have in our substituted Locke solutions, might also combine with the blood plasma and thus lose its physiological properties.

To test this, mixtures were made of normal pig's serum with various Locke solutions, and the pharmacological action of such mixtures studied on heart and blood vessels.

It was found that the action of potassium or sodium ions is not at all inhibited by the blood serum, the effect of iodine ions however may be completely obliterated. Thus a Locke solution in which the NaCl was wholly substituted by its equimolecular weight of NaI, is a powerful vaso-constrictor and cardiac stimulant. If, however, such a solution be mixed with two parts of serum, the effect of iodine is entirely inhibited, and the action on heart and vessels is the same as that obtained with normal Locke solution and serum mixed in the same proportions (Fig. 8A). The *iodine* ions have combined with the plasma. A larger proportion of iodine ions mixed with serum leaves some

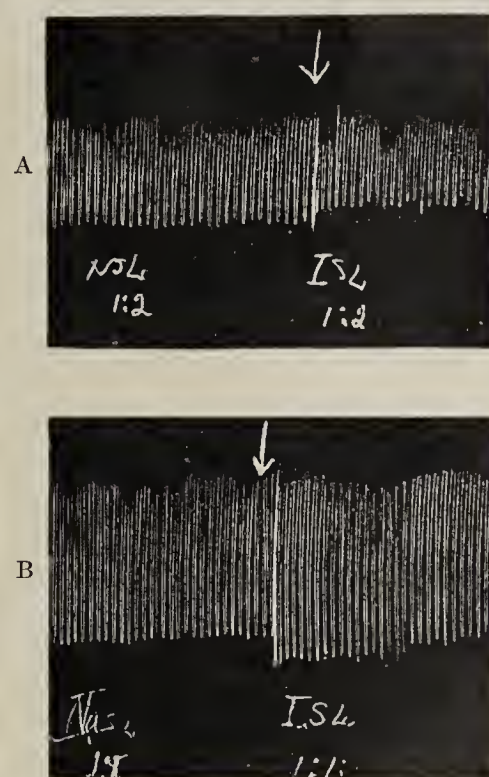


FIG. 8.—Frog's heart; suspension method. Systole = downstroke.

A.—Normal Locke, plus normal serum 1:2, and iodine Locke, plus normal serum 1:2.

B.—Normal Locke, plus normal serum 1:1; normal Locke, plus normal serum 1:1.

of the iodine uncombined and hence produces a slight stimulation (Fig. 8B).

DISCUSSION AND SUMMARY.

From the above experiments it will be seen that the potassium ion produces a relaxation of the blood vessels and a marked depression of the heart; that the sodium ion has a slightly stimulating action on the blood vessels and also stimulates the heart, and that the iodine ion is a powerful stimulant to both the heart and blood vessels as shown by its action in experiments on isolated organs. The stimulating effect of the iodine ions, however, is greatly inhibited in the intact animal by their chemical combination with the proteids of the blood.

Whether the chemical compound thus produced is a stable one, or whether it is a loose one, and slowly breaks up, setting iodine free, remains an open question. If iodine is set free, a stimulating effect is to be expected.

The action of sodium and potassium iodides on the heart and vessels can be best understood from the action of their component factors. Sodium iodide possesses no depressing property, for the sodium ion is a vascular constrictor and a cardiac stimulant, and the iodine ion, in so far as it is free to act, has the same action.

Potassium iodide, on the other hand, clearly shows the depressing effect of the potassium ion on the heart and vessels, especially of mammals, not only on isolated organs, but also in the living animals. It is therefore not a matter of indifference which of the iodides is to be chosen for the purpose of depressing the circulation, as, for instance, in case of an aneurism. The above pharmacological analysis of the action of the iodides, furthermore, shows that so far as experimental evidence goes, the iodides possess no special virtue of lowering blood pressure, but that that effect is really due entirely to the potassium, and could be produced even more efficiently by other potassium salts.

Addendum: After this paper went to press, two publications appeared which are interesting to note in this connection. A. Lehdorff in the *Arch. f. Exp. Path. u. Ther.*, Vol. 76, p. 224, calls attention to the stimulating action of iodine on the blood-vessels; and J. Sehwalbe in the *Deut. Med. Wochenschrift*, Nos. 14 and 15, 1914, summarizes the opinions of the

most prominent German clinicians on the use of iodides in arteriosclerosis, the weight of opinion being unfavorable to the drug.

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NOTES ON NEW BOOKS.

A Text-Book of Medical Entomology. By WALTER SCOTT PATTON, M. B., etc., and FRANCIS WILLIAM CRAGG, M. D., etc. £1-1-0. (London, Madras and Calcutta: Christian Literature Society for India, 1913.)

This volume is the outgrowth of the rich experience of these authors at the King Institute at Madras, India. By a fortunate arrangement of material, it will serve, not only as an advanced text-book, but also as a valuable reference work.

In considering the relationship between insects and disease, proportionally more space has been given to the entomological features than to the medical aspects of the subject. A very comprehensive description is given of the blood-sucking arthropods, not only of India, but throughout the world. The types described are not restricted to those of recognized importance on the liberal basis that "a certain breadth of view is essential to progress." Especial attention is given to Williston's North American Diptera and to the work of Banks and Stiles on American Ticks.

In the section on practical laboratory methods, careful attention is given to the methods of rearing and infecting insects and to the anatomical examination for evidences of infection. From their wide experience in this subject the authors are able to give extremely helpful details which, though they are of a minor nature, are often so essential to success.

This volume is of especial interest to the investigator. It abounds in original material. Numerous pitfalls of experimental work are pointed out and a careful consideration is given to the methods of avoiding confusion between the natural protozoan fauna of insects and pathogenic parasites.

To the person approaching the subject from purely the medical standpoint, it might be possible to make the subject matter a little more accessible. For instance, it seems a little unexpected not to find such diseases as malaria, bubonic plague, or dengue, mentioned in the index, though omissions in an index of the first edition of a work should perhaps not be mentioned.

The volume is profusely illustrated with clear black and white drawings. In all there are probably more than 500 figures. To the medical man it might add a little interest to represent lesions in insects produced by parasites such as the organisms of malaria or representations of the stage of the life cycle of the parasites during their development in the invertebrate host.

The authors have condensed an immense amount of accurate information into a very convenient form. It is the most comprehensive work on this subject and has a very wide field for its application.

An Introduction to the History of Medicine. With medical chronology, bibliographic data and test questions. By FIELDING H. GARRISON, A. B., M. D., Principal Assistant Librarian, Surgeon-General's Office, Washington, D. C. Illustrated. 763 pp. 8°. (Philadelphia and London: W. B. Saunders Company, 1913 (1914).)

This book marks an epoch in American medical literature. Not only does it register the contributions of a newer civilization in their proper historical relation to those of the world at large, but in it for the first time an American writer, in fulfillment of an evident want, offers a comprehensive treatise of a universal history of medicine.

This book, fitly dedicated to the librarian of the Surgeon-General's Office, Colonel Walter D. McCaw, does not pretend to be more than an introduction into the vast fields of medical history. The author wishes, as he says himself, to act only as an interpreter of "the best that has been thought and said," and not to attempt a learned or lengthy exposition. It may be stated right here that his book fulfills his aim admirably and that it offers even more than its modest title indicates. The clearness, conciseness and perspicacity of its statements, the accuracy of its references alone will insure a permanent value to this book. A detailed analysis is obviously impossible, for although intended only as an introduction, the amount of material brought together is stupendous. It treats effectively the various aspects of medical endeavor from earliest times to our own days, a range which more pretentious books have not been able to cover. One would presume *à priori* that such a guide through the immense records of the past within a limited space must be of necessity a dry-as-dust enumeration of persons, discoveries and other prominent features. By a very happy combination of talents, those of the historian, physician and narrator, the author has been able to elude this presumption successfully. Wherever one opens the book one is captivated at once by the easily flowing narrative which takes one *in medias res* without unnecessary preamble. The men of mark stand out in bold relief, often visualized by superb portraits, which evidence most careful selection. The characteristics of a given period with its fitful changes of method, the fall and rise of opinions and doctrines, their intrinsic importance and proper correlation to cultural conditions are handled with fine circumspection. No profound psychologic or philosophic analysis is attempted and still the matter is presented in a way which stimulates thinking, comparison and further study. With rapid, telling strokes the main features are given, and, as a sketch from a skillful brush often presents by that greater art of judicious elimination a more striking likeness to reality than the finished picture, so the perusal of this book leaves in the reader's mind more distinct and easily remembered impressions than the more elaborate exposition in greater works. Especially successful is the biographical treatment of the various pathfinders and epochmakers in medical history. The sketches of Harvey, Boerhaave, Haller, Pasteur, Virchow and others, though by no means only echoing traditional opinions, are little masterpieces to which casual anecdotes lend a peculiar charm and color. The finely thoughtout chapter on the identity of all forms of ancient and primitive medicine, the introduction to the one on Greek medicine, the one on the 17th century as the age of individual scientific endeavor, on the beginning of organized advancement of science in the 19th and of organized preventive medicine in our century, offer much thought and inspiration, even to those who will perhaps differ in the just assignment of values. No one, not even the most "practically" inclined practitioner, if he reads at all, can lay the book aside without feeling lifted above the drudgery of daily routine, without a warmer interest in the aims of his art and science; and, perhaps somewhat humbled in his overestimation of current advances, he will become conscious of that almost intangible bond of human kinship between those of all times who have made the relief of pain and disease their task.

As regards the form, the technical construction of the book, it evinces everywhere that methodical procedure which so notably distinguishes the bibliographic productions of the great national institution in Washington. Ample and accurate references, chronological tables, subject and author indices, suggestions for collateral reading are provided and offer, without disturbance to the casual reader, most valuable assistance to the student and to those desiring a ready reference book on historical questions. Certain errors and omissions in a work like this are unavoidable; one can only wonder that there are so few considering the bewildering mass of data, names and facts which had to be sifted.

Other editions of this book, and many we hope may be called for, will efface such slips, which hardly affect the great usefulness of the work as it stands. I cannot refrain, in conclusion, from noting that the book has already received a warm commendation from Prof. Karl Sudhoff. No other review can offer a greater encouragement to the author than this unstinted praise from the acknowledged leader in scientific historical research. It is to be hoped that Sudhoff is right when he thinks that in English-speaking countries the book will do more good and make more converts for historical thinking than the greater standard works.

A few misprints have been noted:

P. 301, 20 lines from top, for 1162 read 1762.

P. 307, 7 lines from top, for University of Virginia read Williamsburg, Va.

P. 637, 5 lines from top, for Annemese read Annemasse.

P. 649, 2 lines from bottom, for 1890 read 1876.

A. C. K.

International Clinics. Vol. I. 24th Series. Edited by HENRY W. CATTELL, M. D., and associates. \$2. (Philadelphia and London: J. B. Lippincott Company, 1914.)

This volume opens with two noteworthy papers by Philadelphia physicians, the first by Willson on "The Treatment of Nephritis," and the second by Taylor on "Cardiovascular-renal Regulation by other Means than Drugs," and closes with an interesting review of the "Progress of Medicine" during 1913. Between these are interspersed other papers to appeal to specialists in various branches of medicine and surgery.

Diseases of the Heart. By JAMES MACKENZIE, M. D., F. R. C. P., etc. Third Edition. (London: Henry Frowde and Hodder & Stoughton, 1913.)

I note with pleasure the appearance of the third edition of this interesting and stimulating book by the great pioneer in the field of modern cardiac and vascular diseases. Though the body of the work is not much altered, much more use is made of the knowledge gained by means of the electrocardiograph than in the previous editions. The book is considerably enlarged and enriched from the tremendous store of clinical cases studied with an unparalleled thoroughness and precision under Dr. Mackenzie's personal observation and is fuller than ever of excellent suggestions for clinical practice. It is a compilation of the original views and practices of Dr. Mackenzie and is in no sense a systematic text book to present the entire field of cardiac diseases. The reader should not approach the book with this expectation.

Especially noteworthy is the emphasis that Mackenzie lays upon the fact that digitalis is ineffective where the heart muscle has suffered from bacterial or other intoxications, which is often realized more in theory than in practice. The chapter upon the use of digitalis in auricular fibrillation is especially interesting.

The brilliant style of the author and the excellent typographical work of the publishers, which added much to the previous editions, are pleasing features of this one as well.

A. D. H.

Progressive Medicine. Edited by HOBART AMORY HARE, M. D., etc. Vol. I. (Philadelphia and New York: Lea & Febiger, March, 1914.)

This volume is shared by surgery, medicine, diseases of children, rhinology, laryngology and otology; and in each chapter the compilers present clearly and concisely the latest views as held by the leading specialists on many diseases and conditions. The résumés are well done and are intended to serve merely as guides for busy practitioners who may not be able to use the original sources, or who have too large a clientèle to find time for exhaustive reading.

THE QUARTER CENTENNIAL ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL AND THE TWENTY-FIRST ANNIVERSARY OF THE OPENING OF THE MEDICAL SCHOOL

Will be observed by appropriate exercises beginning October 5, 1914, and continuing during the week.

The exercises upon Monday, October 5, 9.30 a. m. to 12 m., are to be especially arranged for by the Training School for Nurses and will be announced later.

Upon Monday at 3.30 p. m., the formal opening meeting will be held at the Lyric, with addresses by Dr. W. H. Welch, Sir William Osler, Miss M. Adelaide Nutting and Dr. H. M. Hurd.

In the evening there will be dinners of the former Medical Officers of the Hospital, and of the Alumnae of the Training School for Nurses.

Upon Tuesday, October 6, 9.30 a. m. until 12 m., papers upon medicine by former members of the staff will be presented in the Medical Amphitheatre. Papers or demonstrations of methods of study of Psychiatry at the Henry Phipps' Clinic from 10 a. m. to 12 m. Gynecological operations in the Surgical Amphitheatre from 10 a. m. until 1 p. m. A Clinic by Sir William Osler at 12 m.

Luncheon at the Hospital from 1 to 2.30 p. m.

From 2.30 to 3.30 p. m. Clinic in the Harriet Lane Home by Dr. John Howland. At 3.30 p. m., a dedication of the Hewetson Medallion.

A demonstration of Nurses' work in the Medical Amphitheatre from 4 to 5 p. m.

From 4.30 to 5.30 p. m., a lecture on the Herter Foundation by Dr. Thomas Lewis of London.

In the evening a Dinner of the Alumni of the Medical School.

Wednesday, October 7, from 9.30 a. m. to 1 p. m., Surgical Operations in the Surgical Amphitheatre.

From 11 a. m. to 1 p. m. Visits to Medical Laboratories.

1 p. m., Luncheon.

At 3.30 p. m., Dedication of the James Buchanan Brady Urological Clinic, with addresses by Dr. Winford Smith, President Goodnow of The Johns Hopkins University, Dr. H. H. Young, and others.

A Garden Party upon the lawn of the Hospital at 5 p. m.

In the evening a Subscription Dinner to Mr. James Buchanan Brady. Also Class Dinners.

Thursday, October 8, 9.30 a. m. to 1 p. m., Papers in Pathology in the Medical Amphitheatre.

Also Papers or Addresses upon Obstetrical Topics in the Surgical Lecture Room, 10 a. m. to 12 m. Operations in Urological Surgery in the Surgical Amphitheatre, 10 a. m. to 12 m.

1 to 2.30 p. m., Luncheon.

4.30 p. m., Second Herter Lecture by Dr. Lewis.

In the Evening, Class Dinners.

Friday, October 9, 4.30 p. m., Third Herter Lecture by Dr. Lewis.

More detailed programmes will be published later.

During the Anniversary Week laboratory demonstrations will be given in the laboratories of the Medical School as follows:

In the Anatomical Laboratory, By Prof. Mall and the Anatomical Staff.

In the Physiological Laboratory, By Prof. Howell and the Physiological Staff.

In the Pharmacological Laboratory, By Prof. Abell and the Pharmacological Staff.

The exact dates and hours of such demonstrations will be announced in the final program.

PROGRAMME FOR THE CELEBRATION OF THE TWENTY-FIFTH ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL

MONDAY October 5	TUESDAY October 6	WEDNESDAY October 7	THURSDAY October 8
9.30-12 Nurses' Training School	9.30-12 Medicine (Medical Amphitheatre) Psychiatry 10-1 Gynecology (Surgical Amphitheatre) 12 Clinic Sir William Osler	9.30-1 Surgery (Surgical Amphitheatre) 11-1 Medical Laboratories	Pathology (Medical Amphitheatre) Obstetrics (Surgical Lecture Room) 10-12 Urological Surgery (Surgical Amphitheatre)
	1-2.30 Luncheon	Luncheon	Luncheon
3.30 Opening Meeting (The Lyric) Addresses: Dr. W. H. Welch presiding Sir Wm. Osler Dr. H. M. Hurd Miss M. A. Nutting	2.30 Pediatric Wards Dr. Howland 3.30 Dedication Hewetson Medallion 4.30 Herter Lecture	3.30 Dedication of the J. B. Brady Urological Clinic Dr. W. H. Smith presiding Pres. F. J. Goodnow Dr. H. H. Young and other speakers 5 Garden Party (The Lawn)	4.30 Herter Lecture
Dinners Johns Hopkins Hospital Alumni Nurses	Dinner Alumni of Medical School	Dinner to Mr. J. B. Brady, Donor of the new Urological Clinic Class Dinners	Class Dinners

THE HERTER LECTURES FOR 1914.

The Herter Lectures will be given in connection with the Quarter Centennial Anniversary of the Opening of The Johns Hospital and the Twenty-first Anniversary of the Opening of the Medical Department of The Johns Hopkins University, upon Tuesday, Thursday and Friday, October 6, 8 and 9, 1914, at the Physiological Lecture Room, Monument and Washington Streets, at 4.30 p. m., by Thomas Lewis, M. D., University College, London, England.

Dr. Thomas Lewis in charge of the heart station at University College, and Editor of *Heart* has done important work in the study of cardiac conditions, and will present three lectures on the scientific study of the heart and its bearing on clinical medicine. He is the first clinical investigator who has filled the position of Herter Lecturer. The titles of his lectures will be announced later.

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EXPERIMENTAL OBSERVATIONS ON THE SUPRARENAL GLANDS WITH ESPECIAL REFERENCE TO THE FUNCTIONS OF THEIR INTERRENAL PORTIONS.

By S. J. CROWE and GEO. B. WISLOCKI, Baltimore.

(From the Hunterian Laboratory for Experimental Surgery.)

Notwithstanding the numerous investigations which have been undertaken since the time of Thomas Addison and Brown-Sequard, but little is known regarding the physiology of the normal suprarenal bodies, or the symptomatology resulting from lesions of these glands. Experimental and clinical studies, however, have shown that the suprarenals are necessary to life; that they are of importance in the regulation of carbohydrate metabolism; and that the secretion of the medullary cells contains a non-proteid substance (adrenalin) which produces, when injected even in minute quantities, a marked rise in blood pressure and a contraction of most of the muscular structures which receive their nerve supply through the sympathetic. It has also been shown that the action of adrenalin on these organs is, in many respects, similar to the effect produced by an electrical stimulation of the sympathetic nerves supplying them.

Such facts as the pigmentation of Basedow's disease; the hypertrophy of the medulla of the adrenals after removal of the thymus; the hypertrophy of the lymph glands and thymus in association with tuberculosis of both the suprarenal glands, together with some of the results of experimental studies on the metabolism of the sugars, all suggest an inter-relation between the suprarenals, thymus, thyroid, lymphatic system and pancreas. In several instances autopsy has disclosed an adenoma of the cortical cells of the suprarenal capsules in children in whom the most striking clinical symptoms were a precocious development of the sexual organs, an overgrowth of hair on the body and an abnormal deposit of fat. Further

evidence of a relationship between the adrenals and the sexual apparatus is afforded by the enlargement of these glands during pregnancy. The increase in size of the adrenals during pregnancy is due to the hypertrophy of the cells of the cortical layer; the chromaffin cells are but little changed.¹ Furthermore, the cells of the corpus luteum are morphologically and histologically similar to those of the zona fasciculata of the adrenal, and it has been suggested that the corpus luteum of pregnancy is really a "temporary cortical suprarenal."² It has also been stated that the complete extirpation of both adrenals in a pregnant animal is not fatal; if the corpus luteum cells, however, are removed at the same time, the animal will not survive.

A suprarenal gland, like the hypophysis cerebri, is composed of two main divisions, which are histologically and embryologically distinct. A *total extirpation* of both the suprarenal bodies is, in most animals, speedily followed by symptoms of muscular prostration, tremors, subnormal temperature, and within a few days by death. On account of the widespread distribution of the *chromaffin system*,³ it is impossible to study

¹ This statement is made by Biedl, but disputed by Wiesel and others.

² Rolleston: The Goulstonian Lectures on the Suprarenal Bodies. Brit. Med. Jour., 1895, Vol. I, p. 629.

³ The paraganglia along the abdominal sympathetic chains and the organs of Zuckerkandl all contain cells histologically identical with those in the medulla of the adrenal, and their extracts have been found to contain a blood-pressure raising principle similar to adrenalin.

the effects of a total removal of this type of tissue alone. There is conclusive evidence, however, that animals deprived of the *entire cortical portion* of both adrenals will not survive, even though the medullary portion remains intact. This was strikingly shown by Biedl⁴ in 1899, while working at the Zoological Station in Naples. In some species of fish the cortex and medulla of the suprarenal glands are separate bodies; a median or interrenal body is made up of cortical tissue alone, while the medullary portion is represented by a series of quite separate bodies which lie in close relationship to the ganglia of the sympathetic chain. In such fishes the extirpation of the interrenal body, leaving the medullary tissue intact, results quite regularly in death within three weeks, the only symptom being a progressive muscular weakness. If a small portion of the cortical tissue is left, however, the fish will recover; and at the end of four weeks this remaining fragment shows a marked hypertrophy, both grossly and microscopically.

Experiments on mammals have shown that an animal may survive the removal of both suprarenal glands for an indefinite period, provided accessory tissue is present. In many instances, this accessory tissue consists of cortical cells alone; it undergoes hypertrophic changes following the removal of both suprarenal glands; and the animal promptly succumbs when this accessory gland is removed.

In general, then, the medullary portion of the adrenal may be compared with the posterior lobe of the hypophysis, and the cortical part of the adrenal with the anterior lobe of the hypophysis. Acromegaly is apparently due to an over-activity of the anterior lobe and is associated with an increase of the eosinophilic cells; while general systemic disturbances of growth and the delayed acquirement of secondary sexual characteristics are referable to an insufficiency of this portion of the gland. On the other hand, definite changes in carbohydrate metabolism result from experimentally produced insufficiency of the posterior lobe, while injection of posterior lobe extracts greatly accelerates metabolic processes—leading to a lowering of carbohydrate tolerance (often to the point of spontaneous glycosuria) and, if long continued, to marked emaciation.

Addison's disease, with the asthenia, pigmentation of the skin, low blood pressure and gastro-intestinal disturbances, is ascribed to the destruction of a large portion of the chromaffin system (Wiesel), usually due to tuberculosis. As was previously mentioned, an hypertrophy of the sexual organs, adiposity, and an overgrowth of hair on the body have been the striking symptoms in children with an adenoma of the cortical portion of the adrenals, but aside from this and a similar suprarenal virilism or hirsutism met with in adults,⁵ the writer knows of no syndrome which has been ascribed to either an over or under activity of this part of the gland. On account of the great size of the cortex of the adrenal in the foetus,⁶ the his-

tological structure of this portion of the gland, its hypertrophy during pregnancy, and the experimental demonstration that it is the cortex of the adrenal which is necessary to life, all make it seem possible that careful experimental studies may show that this portion of the adrenal is as important a member of the ductless gland series as is the anterior lobe of the hypophysis.

Furthermore, there seems to be a quite definite relation between the suprarenal bodies, the thymus and the lymphatic system. Although this relationship is not emphasized in any of the text-books or special articles we have seen dealing with the physiology and pathology of the adrenals, there are as many as fifty clinical cases to be found in the literature of the past ten years with titles such as: "An Unusual Case of Addison's Disease with a Status Lymphaticus;" or, "A Case of Status Lymphaticus with a Complete Destruction of the Medulla of the Adrenals." It will be shown later that we have been able to produce a condition in animals which closely simulates a true status lymphaticus.

It was with these general points in mind that the following experiments were undertaken. Up to the present time we have made observations on 26 animals. It was our purpose to study the immediate and remote effects of (1) a total removal of both the suprarenal bodies in young and in old animals; (2) an adrenal insufficiency produced by the operative removal of portions of the gland at intervals of weeks or months. In the dog, a good exposure of the adrenals may be obtained either through a right or a left rectus incision, and the desired amount removed, or the adrenal (lumbar) vein ligated, without loss of blood or injury to the neighboring structures. We have made no attempt at the operation to separate the cortex from the medulla, and in the following observations the portion of the gland removed always includes both cortex and medulla.

The results of our experiences may be considered under the following headings:

- I. The effects of a total removal of both suprarenal bodies.
- II. The effects of removal of either the right or the left adrenal alone.
- III. The relative importance of the cortex and medulla of the adrenal.
- IV. The relation of the adrenal to carbohydrate metabolism.
- V. Transplantation of the adrenals.
- VI. The possible relation between the suprarenal bodies, the thymus and the lymphatic system.

I. THE EFFECTS OF A TOTAL REMOVAL OF BOTH SUPRARENAL BODIES.

We have removed both suprarenal glands either at one operation or by successive stages in nine animals, and are able to fully confirm the observations of Biedl and others, that in the dog the suprarenal bodies are necessary to life. Abelous and Langlois⁷ have found that in frogs, guinea-pigs and rabbits:

⁴ Biedl: *Innere Sekretion*, 1913, I. Teil, p. 376.

⁵ Wiesel, J.: *Krankheiten der Nebennieren*. Lewandowsky's *Handbuch der Neurologie*, Band IV, Pt. iii, 375.

⁶ Refer to article by Elliott and Armour: *The Development of the Cortex in the Human Suprarenal Gland and its Condition in Hemicephaly*. *Jour. Path. and Bact.*, 1911, Vol. XV, p. 481.

⁷ Abelous and Langlois: *Note sur les fonctions des capsules surrénales chez la grenouille*. *Compte rend. de la Soc. Biol.*, 1891, Vol. XLIII, pp. 792-800. *La mort des grenouilles après la destruction des deux capsules surrénales*. *Compte rend. de la Soc. Biol.* 1891, XLIII, pp. 855-859.

total extirpation of these glands is always fatal; in case of survival, a careful search will invariably reveal hypertrophied accessory adrenal tissue.⁸

On account of the size of the animal and the comparatively infrequent occurrence of accessory tissue, all of our experiments have been made on the dog. We have tried to determine:

(A) The influence of age and sex on the length of life after a total removal of both adrenals.

(B) The length of life after:

(a) Total removal of both adrenals at one operation.

(b) Gradual ablation of both adrenals by successive operations.

(C) The circulatory disturbances resulting from a total removal of both adrenals at one operation.

(D) The general manifestations of adrenal insufficiency.

(A) We have been unable to show that the age and sex of the animal has any influence on the results of the operation. Although one of the younger animals (Observation 5), a female, aged 6 months, succumbed on the eighth day; and another (Observation 15), a male, aged 6 months, survived four days, the average length of life in the remaining eight observations was less than twenty-four hours. In general, the younger animals succumb more promptly than do the older ones; frequently they will not survive a partial extirpation of the adrenals, although as much as one-fourth of one gland is left. This was rather surprising to us, since our observations on experimental hypophysectomy in the canine⁹ show that the age has a definite influence on the length of life after a total removal of the hypophysis. Of thirteen total hypophysectomies on adult animals, the average period before death was two days; while the average length of life of the eight puppies in which the same operative procedure was carried out was 11 days.

It has been stated that a total extirpation of both adrenals is not fatal in a pregnant animal, the function of the cortex of the adrenal being taken up by the cells of the corpus luteum.

⁸ These accessory bodies may be miniature adrenals composed of epithelial and chromaffin tissue; or they may be made up of epithelial (cortical) cells alone. They are rarely present in dogs and guinea-pigs, but are very commonly found in rabbits and rats, making these latter animals unfit for experimental studies.

The following are the various situations in which accessory adrenal bodies may be found:

1. In the vicinity of the adrenals, lying in connective tissue as an independent body.

2. Under the capsule or in the substance of the kidneys.

3. Between the vena cava and aorta, or in the walls of the blood-vessels (suprarenal artery and vein, vena cava, renal vein).

4. In the sympathetic ganglia.

5. Between the transverse colon and spleen, in the ligamentum mesocolon transversum.

6. Under the capsule or in the right lobe of the liver.

7. In the pancreas.

8. In the retroperitoneal tissue; in the region of the sacro-iliac synchondrosis; along the entire vas deferens; between the testicle and the epididymis; in the broad ligaments; along the Fallopian tubes and in the ovaries.

⁹ Crowe, Cushing and Homans: Experimental Hypophysectomy. The Johns Hopkins Bulletin, 1910, Vol. XXI, pp. 127-169.

We have, as yet, made no studies on pregnant animals, but some very suggestive experiments along this line were made in 1912-13 by Harvey and Stewart.¹⁰

We may conclude, therefore, in agreement with many other investigators, that the suprarenal glands are of vital importance. If they are removed the animal invariably succumbs, regardless of the age or sex, provided there is no accessory adrenal tissue to take up their function.

(B) It apparently makes but little difference in the length of life of the animal whether both adrenals are removed at one operation, or whether there is a gradual depletion by successive operations at intervals of weeks or months. In other words, it seems that there is no other tissue, with the exception of accessory bodies, that is capable of taking up the function of the adrenals, or at least not to a degree sufficient to prevent a fatal outcome when the last remaining fragment of the suprarenal gland is removed.

Table I will demonstrate this point.

(C) I am indebted to Dr. Wm. H. Howell for the following notes concerning the circulatory disturbances after a total removal of both adrenals. The animals were given an anæsthetic, artificial respiration instituted and a continuous kymographic record made of the blood-pressure, pulse-rate and respiration for seven or eight hours following the removal of the suprarenal bodies. His conclusions are as follows:

(1) The immediate effect of the operation was a fall of mean blood-pressure (about 30 to 40 mm.) and a great increase in heart-rate. This latter effect is frequently seen after any abdominal operation, and is possibly not specific.

(2) For about three hours after the operation, the blood-pressure remains steady after a preliminary rise of 15 to 20 mm., while the pulse-rate steadily grows more rapid.

(3) After the fourth or fifth hour, the pressure rather abruptly begins to fall while the pulse-rate continues to grow more rapid.

Both the main facts noted, namely, the steady increase in heart-rate,¹¹ beginning practically at once after the operation, and the final somewhat suddenly appearing but gradually increasing fall in blood-pressure, would seem to meet a rational explanation on the view of a gradual disappearance of epinephrin from the circulation.

(D) The general symptoms which appear after a total removal of both adrenals are in many respects similar to those produced by a total hypophysectomy. As a rule, the animal promptly recovers from the anæsthetic and for several hours is in an apparently normal condition. He then begins to show a loss of appetite; symptoms of muscular weakness; and, what is most striking, a gradually increasing drowsiness. These animals act as if they had been given a large dose of morphia. There is a lowering of the body temperature, as low as 25° C.

¹⁰ Not published.

¹¹ It was called to my attention by Dr. L. F. Barker that in some clinical cases of tachycardia the heart-rate seems to be slowed after the administration of adrenalin solution by mouth several times a day for a period of two or three weeks.

in some cases, and an accompanying muscular rigidity with tremors. The rigidity and tremors will disappear temporarily if the animal is wrapped in warm blankets and the body temperature raised by this means to the normal level.

In several of our animals there has been a series of general convulsive seizures preceding death. This symptom seems to

parently normal for the succeeding eight months of observation (cf. Fig. 9, dog II). These findings suggest that some cases of clinically idiopathic epilepsy may be due to a disturbance of function, either of the cortex of the adrenals or of the chromaffin system.

The following protocol, together with a kymographic record

TABLE I.
TOTAL REMOVAL OF BOTH ADRENALS.

	Weight.	Operations.	Duration of Life.	Remarks.
Obs. 2. Male, age 6 mos.	Oct. 30, 1912. 11¾ lbs.	Oct. 30, 1912. 9/10 of rt. adrenal removed.	Interval of 7 days between 1st and 2d op'n.	Apr. 28, 1913. Convulsions beginning 18 hours after removal of all but a fragment of adrenal tissue, and recurring at intervals for a week.
	Mar. 5, 1913. 19 lbs.	Nov. 6, 1912. Left adrenal removed.	Interval of 172 days between 2d and 3d op'n.	
	Apr. 1, 1913. 21 lbs.	Apr. 27, 1913. Portion of remaining hypertrophied fragment of rt. adrenal removed.	Interval of 187 days between 3d and 4th op'n.	
	Apr. 30, 1913. 20 lbs.			
	Oct. 8, 1913. 27¼ lbs.	Nov. 10, 1913. Removal of remaining rt. adrenal.	Interval of 18 hours between 4th op'n and death.	
	Nov. 10, 1913. 29¾ lbs.			
Obs. 3. Male, age 1 yr.	Mar. 30, 1913. 28½ lbs.	Nov. 13, 1912. 9/10 of rt. adrenal removed.	Interval of 7 days between 1st and 2d op'n.	Although there was a viable transplant of six months' standing, it proved to be of no functional value.
		Nov. 20, 1912. Entire left adrenal removed.	Interval of 175 days between 2d and 3d op'n.	
		May 14, 1914. Fragment of rt. adrenal removed.	Interval of 24 hours between 3d Op'n and death.	
Obs. 5. Female, age 6 mos.	Feb. 5, 1913. Both adrenals removed.	Death after 8 days.	Feb. 10, 1913. 60 cc. urine for 24 hours. Dull and listless. Feb. 11, 1913. Pulse 125. Temp. 36.1°. Refuses food. Feb. 12, 1913. Pulse 115. Temp. 31.6°. Very weak and unsteady on feet. 85 cc. urine voided during past 24 hours.
Obs. 6. Female, age 2 yrs.	Feb. 10, 1913. 7 lbs.	Feb. 10, 1913. Both adrenals removed.	Death after 24 hours.	
Obs. 13. Male, age 6 mos.	Apr. 13, 1913. 19¾ lbs.	Apr. 13, 1913. Left adrenal removed.	Interval of 35 days between 1st and 2d op'n.	
		May 18, 1913. Rt. adrenal removed.	Interval of 12 hours between 2d op'n and death.	
Obs. 14. Female, age 6 mos.	Apr. 20, 1913. 12¼ lbs.	Apr. 20, 1913. Left adrenal removed.	Interval of 7 days between 1st and 2d op'n.	
	Apr. 30, 1913. 12 lbs.	Apr. 27, 1913. ⅔ rt. adrenal removed.	Interval of 7 days between 2d and 3d op'n.	
		May 4, 1913. Remainder of rt. adrenal removed.	Interval of 24 hours between 3d op'n and death.	
Obs. 15. Male, age 6 mos.	May 4, 1913. 18½ lbs.	May 4, 1913. Left adrenal and 9/10 of rt. removed.	Interval of 21 days between 1st and 2d op'n.	After 2d operation. Listless; will not voluntarily take food; subnormal temperature.
		May 25, 1913. Remaining hypertrophied fragment of rt. adrenal removed.	Interval of 4 days between 2d op'n and death.	Carotid pressure 45 mm.; tendency to anuria.
Obs. 16. Female, age 3 mos.	May 12, 1913. Both adrenals removed.	Death after 12 hours.	This animal was used by Dr. Howell for observations on coagulations of the blood after extirpation of adrenals.
Obs. 17. Male, age 3 mos.	May 12, 1913. Rt. adrenal and ⅔ of left removed.	Interval of 18 days between 1st and 2d op'n.	
		May 30, 1913. Remaining fragment of left adrenal removed.	Interval of 12 hours between 2d op'n and death.	

be independent of the lowering of the body temperature, and in no instance has the post-mortem examination revealed any gross lesion in the central nervous system. Convulsive seizures have also been observed in animals with an "almost total" removal of both adrenals. In one animal there were frequent convulsive attacks for a week following the last of a series of operations; although only one-tenth of one adrenal was left in situ in this case, the animal finally recovered and was ap-

of the carotid pressure, will serve to illustrate the symptoms and general condition of an animal with adrenal insufficiency.

OBSERVATION 30.—A male fox terrier; age 1 year; weight 16 pounds.

Feb. 22, 1914 (11 a. m.).—An uncomplicated operation through an incision in the right rectus muscle. Removal of the entire right adrenal and all but a minute fragment (purposely left at the upper pole) of the left adrenal. A fragment of the right adrenal,

measuring 6 x 4 x 5 mm., was transplanted between the posterior sheath of the rectus and the transversalis muscle.

A catheterized specimen of urine before operation contained no reducing body, while the urine removed 30 minutes after the operation promptly reduced both Fehling's and Nylander's solutions.

Feb. 23, (2 p. m.).—Very dull; can be roused, but will not take food or milk. If placed on his feet, will slowly and unsteadily walk around the room for a few minutes, but soon lies down and falls asleep. The tongue and mucous membranes are dry, cold and pale. The pupils are contracted, but react normally to light. There is an extreme degree of general muscular rigidity with tremor, and an exaggeration of all the tendon reflexes. The pulse is feeble and irregular. The heart-beat, counted with the aid of a stethoscope, is 96 to the minute. The rectal temperature is 29° C.; respiration 18. There is no vomiting, no diarrhea nor convulsive seizures. By wrapping the animal in warm blankets, the body temperature was raised within one hour to 33.7° C.

This animal seemed entirely insensible to pain; the common carotid artery was exposed and the accompanying kymographic record made without the slightest evidence of discomfort. We have frequently seen animals in this "anæsthetic state" following a total removal of the hypophysis cerebri.

Repeated injections of a 1-1000 solution of commercial adrenalin produced the characteristic cardio-vascular response, but without any evidence of improvement in the general manifestations.

Feb. 24, (10 a. m.).—Comatose; femoral pulse barely palpable. No urine secreted for the past 24 hours. Respiration shallow and irregular; ceased about 11 a. m.

Autopsy.—Made immediately after death. Hemorrhage under the skin and in several of the organs, probably due to the intravenous administrations of adrenalin. What is of especial interest is a beginning disintegration of the remaining fragment of the left adrenal; it is quite apparent that we had cut off its blood supply at the time of the operation. The transplant under the rectus muscle is also going to pieces; certainly, it has been of no functional value.

II. THE EFFECTS OF THE REMOVAL OF EITHER THE RIGHT OR THE LEFT ADRENAL ALONE.

A transient glycosuria occurs quite regularly after any operative manipulation of either the right or the left suprarenal gland. We have examined catheterized specimens of urine in 18 animals, both before and at frequent intervals after the operation. In a large percentage of these animals the glycosuria appears within a few minutes after the operation on the adrenal, and persists from four to twenty-four hours. In some cases the urine contains as much as 40 grams to the liter of a substance which must be glucose, since it reduces Fehling's and Nylander's solution; ferments; forms crystals with phenylhydrazine acetate; and is dextrorotatory. In no instance did the glycosuria persist for more than twenty-four hours, and subsequent estimations of the tolerance for levulose and galactose failed to show any permanent disturbance of carbohydrate metabolism. This whole question will be more fully discussed in a subsequent section of this paper.

Aside from the appearance of a transient glycosuria, our experiences are in accord with those of others, namely: (1) No acute manifestations of adrenal insufficiency follow the removal of either the right or the left adrenal alone; (2) the remaining gland undergoes marked hypertrophic changes, and within a week or ten days after the operation may be almost double the original size. Some observers have noted an hyper-

trophy of the medulla as well as of the cortex. In our series, however, the compensating changes are confined to the cortical layer (Figs. 1 and 2, dog XI, plate I; and Fig. 4).

The thyroid, the hypophysis and the liver have shown no constant changes which may be ascribed to an adrenal insufficiency. We have not studied microscopically the changes in the glycogen content, although there is probably an increased glycogenolysis immediately following any operation on the adrenals. We have also been unable to see any striking changes in the pancreas, although the islets have not yet been studied with Bensley's stain.

The interstitial cells in the testes are not increased in number or in size, and the ovaries look normal.

III. THE RELATIVE IMPORTANCE OF THE CORTEX AND THE MEDULLA OF THE ADRENAL.

The following group of experiments was made in order to determine which portion of the adrenal is of vital importance. The solution of this question is not so simple as was the differentiation of function of the two principal lobes of the hypophysis. It is a comparatively easy procedure to remove either the anterior or the posterior lobe of the hypophysis without interfering with the normal blood supply of the remaining part; this is impossible, however, in the adrenals, due to the anatomical relationship of the medulla to the cortex, and the peculiar arrangement of the blood supply.

It was first pointed out by Stilling,¹² who made some extirpation experiments on rabbits, that when one adrenal is removed the remaining gland undergoes a marked compensatory hypertrophy. He also made the important observation that it is the cortical portion which shows the hypertrophic changes. The extirpation experiments of Biedl upon fish mentioned above seem to demonstrate quite definitely that it is the interrenal or cortical portion of the gland which is of vital importance in this species of animals. Moreover, it has been pointed out by numerous observers, but disputed by others (Neusser and Wiesel¹³), that it is the cortical portion of the adrenals which hypertrophies during pregnancy. Rolleston has stated that the corpus luteum cells in the ovary of pregnant animals are "temporary cortical suprarenal glands," and in case the adrenals are extirpated during pregnancy, the function of the cortex is taken up by these lutean cells, at least to a degree sufficient to prevent the usual fatal outcome.

Our own observations seem to bear out the main contention of Biedl that it is the cortex which is the essential portion of the suprarenal glands. Our reasons for arriving at this conclusion are as follows:

(1) In the embryo the adrenals are relatively huge bodies and are composed mainly of cortical (epithelial) cells. At a later period, cells of the chromaffin system push their way into the center of this mass of cortical tissue, and, when the gland is fully developed, these cells constitute the medulla. Chro-

¹² Stilling; Note sur l' hypertrophie compensatrice des capsules surrénales. Rev. de Med., 1885, VIII, pp. 459-461.

¹³ Neusser and Wiesel. Die Erkrankungen der Nebennieren. Wien, 1910.

maffin tissue, similar in origin and structure to that composing the medulla of the adrenals, may be found on both sides of the abdominal aorta, in the sympathetic ganglia, in the walls of the blood-vessels, and forming definite bodies, such as Zuckerkandl's organs. This extraneous tissue has the same relation to the sympathetic nervous system as has the medulla of the adrenals, and its extracts (Zuckerkandl's organs, for example,) contain a blood-pressure raising principle identical with adrenalin. Aside from its anatomical relation to the cortex, the medulla of the adrenal does not essentially differ from these other chromaffin bodies. In some animals, indeed, this intimate relationship is not present, the cortex being an entirely distinct and separate gland—the interrenal body. In such animals, death promptly ensues after a total extirpation of the interrenal body. If a fragment of this body is left intact, however, it undergoes hypertrophic changes, and the animal does not succumb.

(2) When an adrenal insufficiency is produced by the extirpation of either the right or the left adrenal in the dog, there is, as a rule, a very striking hypertrophy of the remaining gland. The increase in size of the hypertrophied adrenal is due to a rapid multiplication of cells in the cortex, and chiefly in the fascicular zone of the cortex (Figs. 1 and 2, dog XI, plate I). There is little or no enlargement of the medullary portion of the adrenal, as is best demonstrated by comparing, in the gross, a transverse section of the gland removed at operation with the one removed at autopsy several weeks later. Another important change found in the cortex of an adrenal undergoing acute hypertrophy is the variation from the normal in the amount and distribution of the lipoids.¹⁴ These bodies are normally present in all three zones of the cortex, but most abundant in the fascicular zone; particularly in its outer third (Fig. 1, dog XI, plate I). In the hypertrophic gland of two or three weeks standing (Fig. 2, dog XI), the lipoids are most abundant in the glomerular zone; practically absent in the reticular zone; and very scanty in the fascicular zone. This marked disappearance of the lipoids in an adrenal undergoing hypertrophic changes reminds one of the behavior of the colloid in a severe case of Basedow's disease. This analogy may be carried still further, since an hypertrophied adrenal of long standing (examined two or three months instead of two or three weeks after the operation at which the insufficiency was established) frequently has a great excess of lipoids, collected in large irregular clumps and globules. This may, in a rough way, be compared with a colloid goitre.

¹⁴ The technique we have employed for the demonstration of lipoids in the adrenal is as follows:

The stains are prepared by dissolving 2 grams of Na OH in 100 cc. of 70 per cent alcohol; Scharlach R or Sudan III is then added to the point of saturation. Filter into tightly closed staining dishes immediately before using. Frozen sections of the material fixed in 10 per cent formalin are transferred to the stain for 5 or 6 minutes. The sections are differentiated in 70 per cent alcohol for 15 or 20 seconds and washed in water. They are then counter-stained in Ehrlich's hæmatoxylin and mounted in glycerine. If the cover-slip is ringed with paraffin, sections prepared in this way may be kept for two or three years.

(3) A long-standing chronic infection in an animal with an adrenal insufficiency frequently results in the destruction of the parenchymatous cells and a secondary fibrosis throughout the cortex of the remaining fragment of the adrenal. The medulla is but little injured, the chief seat of the lesion being the fascicular zone. Fig. 2, dog VIII, illustrates such a condition. This animal had a low-grade chronic infection of the upper respiratory passages (distemper) which persisted for a month; the terminal event was an acute bronchial pneumonia. The acute infection in this case was the probable cause of the numerous areas of focal necrosis in the fascicular zone. (A section of the normal gland removed at operation is shown in Fig. 1, dog VIII.) We have seen no marked lesion of the medullary portion as a result of an acute or chronic infection. It is of interest to note in this connection that hemorrhages and focal areas of cell necrosis are frequently seen in the cortex of the suprarenals after the subcutaneous injection of diphtheria toxine. This is particularly true in guinea-pigs, and has often been noted in clinical cases dying of some acute general infection.

These findings suggest that some of the symptoms present in clinical cases with acute or chronic infections may be referable to an insufficiency of the cortex of the adrenals, and that a rational therapeutic measure in such cases would be the administration of an extract prepared from the *cortex* of the adrenals. Further observations will be necessary to determine whether or not this theory is tenable.

(4) The illustration (dog III, plate I,) shows a complete distintegration of the cells of the fascicular or mid-cortex zone with a striking hypertrophy of the glomerular portion and an approximately normal reticular zone and medulla. This result was accidentally produced by the ligation of some of the larger vessels supplying a small fragment of one adrenal. By repeated operations, all of the adrenal had been removed with the exception of this small fragment of the upper pole of the right gland. After six months, during which the animal was in apparently perfect health, the larger vessels supplying this remaining hypertrophied fragment were ligated. Symptoms of adrenal insufficiency appeared soon after the operation; for two days the animal had frequent convulsive seizures, a sub-normal temperature and an almost total anuria. Recovery gradually ensued, however, and at a fourth operation the remaining fragment of adrenal was further reduced in size by removing a fragment of its outer (cortical) portion; death followed twenty-four hours later. At the autopsy the adrenal shows the condition described above, and with the exception of a marked lymphatic hyperplasia (to be discussed in a later section), the other organs were normal. It seems quite evident in this case that death resulted from the impaired circulation of the zone fasciculata of the cortex of the adrenal; that the tremendous hypertrophy of the glomerular zone is probably of a compensatory nature; and that the well-preserved medulla, as much as was present at any time during the preceding six months, was not sufficient to keep the animal alive after the destruction of the fascicular zone.

IV. THE RELATION OF THE ADRENALS TO CARBOHYDRATE METABOLISM.

There is already a tremendous literature on the general subject of carbohydrate metabolism disturbances and their relation to lesions of the various ductless glands. It is needless to recount here the various theories and experimental results, since these have been admirably presented in the recent publications of Biedl,¹⁴ Macleod,¹⁵ Cammidge,¹⁶ von Noorden,¹⁷ Eppinger, Falta and Rüdinger,¹⁸ and Goetsch, Cushing and Jacobson.¹⁹

Our object in discussing this question is to show:

- (1) That a transient glycosuria follows any operative manipulation of either the right or the left adrenal.
- (2) This glycosuria response is probably not a result of the direct mechanical stimulation of the sympathetic nerves in the neighborhood of the glands; nor is it due to an increased output of adrenalin from the medullary portion of the adrenal.
- (3) There is little or no permanent disturbance of the carbohydrate metabolism in animals with an adrenal insufficiency.

Table II is intended to show that any operative procedure on either the right or left adrenal; massage of the adrenal; and ligation of the lumbar vein (into which the adrenal vein empties) is followed by the appearance of glucose in the urine.

Our conclusion that the glycosuria observed after operation on the adrenal is not due to a direct stimulation of the sympathetic nerves in the neighborhood of the gland is in accord with the observations of Macleod and others.

Macleod showed: (a) that stimulation of the splanchnic nerves will produce a hyperglycemia, provided the adrenals and their blood supply are intact; (b) stimulation of the left splanchnic nerve after ligation of the left adrenal vein was followed by a hyperglycemia in only one of three observations; (c) stimulation of the left splanchnic nerve after the removal of the left adrenal does not produce a hyperglycemia; (d) after complete severance of the hepatic plexus of nerves, stimulation of the splanchnic nerve (with the adrenal intact) does not cause the usual degree of hyperglycemia, whereas electrical stimulation of the peripheral end of the cut plexus is followed by an increased sugar content in the circulating blood.

It seems definitely proven, therefore, that the functional integrity of the efferent nerve fibres to the liver depends on the presence of the suprarenal glands. In our own experiences, any operative procedure on either the right or the left adrenal will cause a glycosuria so long as a minute fragment of the

adrenal remains.²⁰ It is possible to remove, by successive operations, one entire adrenal and as much as seven-eighths of the other with little or no permanent disturbance as a result. The remaining fragment of adrenal often contains medullary tissue that is almost microscopical in size (Fig. 6, dog II), still, any subsequent operative procedure for the purpose of further reducing the size or completely removing this fragment will cause glycosuria. On the other hand, an extensive dissection of the tissue at the site of an adrenal previously removed is never, in our experience, followed by the appearance of sugar in the urine. It seems, then, that the presence of a fragment of the adrenal, however small it may be, is necessary in order to produce this reaction.

The liberation of glycogen in the liver is apparently controlled to a certain extent by a hormone from the suprarenal glands. The intravenous administration of large amounts of commercial adrenalin will cause a glycosuria, as will fright, severe muscular exertion, and other things shown to be associated with an increased outpouring of adrenalin into the circulation. It seems improbable, however, that the small amount of medulla present in the remaining fragment of adrenal in some of our animals could possibly liberate enough adrenalin to produce the glycosuria so constantly found when the fragment is massaged or partially extirpated. If it were otherwise, one would at least expect to find some microscopical evidence of an increased activity of these medulla cells.

(3) The ductless gland control of carbohydrate metabolism constitutes an extremely complicated mechanism, and, as yet, no very satisfactory explanation has been offered as to the origin of many of the experimental and clinical glycosurias. The chromaffin system, including the suprarenal glands on the one hand, and the pancreas on the other, are the two main antagonists; the former accelerating and the latter inhibiting glycogenolysis. The diabetes following extirpation of the pancreas is supposed to be due to the unopposed activity of the chromaffin system. It is impossible to remove the entire chromaffin system, but our experiments on dogs have shown that there is no permanent raising or lowering of the carbohydrate tolerance in animals with only one-sixth or one-eighth of one adrenal remaining. A good example of the influence of an adrenal insufficiency on the carbohydrate metabolism is shown in the tabulated observations on dog II, given below. About four months after the establishment of an adrenal insufficiency, the tolerance for levulose was between 50 and 60 grams; and about 10 grams for galactose. A month later the tolerance for levulose had dropped to less than 20 grams, and for galactose to less than 7 grams. A still greater degree of insufficiency was established by removing a portion of the remaining adrenal; this operation was followed by a transient glycosuria, and one month later the tolerance for levulose had not returned to the normal level. Two observations made about one year after the original operation showed that the tolerance for levulose was certainly *not above the normal*.

¹⁵ Macleod: *Diabetes: Its Pathological Physiology*, 1913.

¹⁶ Cammidge: *Glycosuria and Allied Conditions*, 1913.

¹⁷ von Noorden: *New Aspects of Diabetes*, 1912.

¹⁸ Eppinger, Falta and Rüdinger: *Über die Wechselwirkungen der Drüsen mit inneren Sekretion*. *Ztschr. f. klin. Med.*, 1908, XXVI, 1909, XXVII, 380.

¹⁹ Goetsch, Cushing and Jacobson: *Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri*. *Bull. J. H. H.*, 1911, XXII, 165-190.

²⁰ In observation 8 there was no glycosuria following a total extirpation of the right adrenal.

TABLE II.

OBSERVATIONS ON THE APPEARANCE OF A TRANSIENT GLYCOSURIA AFTER OPERATIONS ON THE ADRENAL.

(For the complete data on these animals, refer to Table IV at end of article).

Operation.	Glycosuria.	Nylan- der's	Feh- ling's.	Fermentation Polariscopic Test.	Remarks.
Obs. 2. Male, age 1 yr. Apr. 27, 1913. Entire left and 9/10 of rt. adrenal had been removed 6 mos. previously. Further reduction of remaining fragment of rt. adrenal.	Transient—appearing 15 minutes after removal of fragment of adrenal.	+	+		
Obs. 3. Male, age 1 yr. Apr. 20, 1913. Removal of left kidney.	No glycosuria	—	—		
Apr. 6, 1913. Ether anaesthesia * for ½ hour. No operation.	No glycosuria	—	—		3 specimens examined; negative during anaesthesia and 1 and 2 hrs. after.
May 9, 1913. Ligation of vessels supplying remaining 1/10 of rt. adrenal.	Transient—lasting 3 hrs.; first appearing immediately after op'n.	+	+		3 specimens examined; positive.
May 14, 1913. Minute fragment of rt. adrenal removed.	Transient—first appearing immediately after op'n.	+	+		1 specimen examined; positive.
Obs. 8. Male, age 2 yrs. Feb. 19, 1913. Rt. adrenal removed.	No glycosuria	—	—	Fermentation — —	Total urine for 6 hours after operation examined; negative.
Obs. 9. Female, age 2 yrs. Pregnant. Feb. 24, 1913. Left adrenal and ⅔ rt. adrenal removed.	Transient—lasting 24 hours.....	+	+		
May 19, 1913. About ¾ of remaining rt. adrenal removed.	Transient	+	+		
Obs. 11. Female, age 1½ yrs. Mar. 31, 1913. Left adrenal removed.	Transient—first appearing immediately after operation.	+	+		
Obs. 12. Female, age 6 mos. Apr. 6, 1913. Left adrenal removed.	Transient—first appearing immediately after operation.	+	+		Specimen examined before operation was negative. 1 specimen examined after op. positive. Urine collected following 12 hrs. was negative.
Obs. 13. Male, age 6 mos. Apr. 13, 1913. Left adrenal removed.	Transient—first appearing 1¼ hrs. after operation.	+	+	Polariscopic 4% Dextrorotary.	2 spec. examined before op'n.; negative. 2 spec. exam. after op'n.; positive.
May 18, 1913. Rt. adrenal removed.	Transient	+	+		Specimen examined before operation reduces slightly. 2 spec. exam. after op'n. give prompt reduction.
Obs. 14. Female, age 6 mos. Apr. 20, 1913. Left adrenal removed.	Transient—first appearing 1½ hrs. after op'n.	+	+		
Apr. 27, 1913. ⅔ rt. adrenal removed.	Transient—first appearing 30 minutes after op'n.	+	+		
May 4, 1913. Remainder of rt. adrenal removed.	Transient	+	+		
Obs. 15. Male, age 6 mos. May 4, 1913. Left adrenal and 9/10 of rt. adrenal removed.	Transient	+	+	Fermentation + +	
May 25, 1913. Remaining fragment of rt. adrenal removed.	Transient	+	+		
Obs. 17. Male, age 3 mos. May 12, 1913. Rt. adrenal and ⅔ of left removed.	Transient—lasting 18 hours.	+	+		
May 30, 1913. Remainder of left adrenal removed.	Transient		+		Spec. examined before op'n.; negative. 1 spec. exam. after op'n.; positive.
Obs. 18. Male, age 1½ yrs. May 25, 1913. Ligation of rt. lumbar vein.	Transient		+		
June 8, 1913. Rt. adrenal removed.	Transient—first appearing immediately after op'n.	+	+		Spec. exam. before op'n.; negative. 1 spec. exam. after op'n.; positive.
Obs. 19. Male, age —. June 8, 1913. Left adrenal massaged for 7 minutes.	Transient—appearing 20 min. after massage.	+	+		
Obs. 20. Male, age ½ yr. Nov. 23, 1913. Rt. adrenal removed.	Transient—appearing ½ hr. after op'n.	+	+		
Dec. 7, 1913. 9/10 of left adrenal removed. Adrenal vein ligated.	Transient—lasting 7 hrs.; appearing 20 min. after op'n.	+	+		1 spec. exam. before op'n.; negative. 2 spec. exam. after op'n.; positive.
Feb. 22, 1914. Dissection in region where rt. adrenal was previously removed.	No glycosuria	—	—		

* Ether anaesthesia was administered in all the operations of this series.

TABLE II.—Continued.

	Operation.	Glycosuria.	Nylan- der's	Feh- ling's.	Fermentation Polariscopic Test.	Remarks.
Obs. 22. Fe- male, age 3 mos.	Nov. 30, 1913. Left adrenal re- moved. Rt. lumbar vein ligated.	Transient—lasting 20 hours.....	+ +	+ +		
	Dec. 14, 1913. 9/10 of rt. adrenal removed.	Transient—lasting 20 hours.....	+ +			
Obs. 23. Male, age 3 mos.	Nov. 30, 1913. Rt. adrenal re- moved. Left lumbar vein ligated.	Transient—lasting 24 hrs. after op'n.; first appearing 15 min. after op'n.	+ +			
	Dec. 14, 1913. 9/10 of left adrenal removed.	Transient—lasting 24 hours.....	+ +			
Obs. 25. Fe- male, age 6 mos.	Feb. 1, 1914. Left adrenal and $\frac{3}{4}$ of rt. adrenal removed.	Transient—lasting 24 hours.....	+ +			
Obs. 26. Male, age 3 mos.	Feb. 1, 1914. Left adrenal and $\frac{3}{4}$ of rt. adrenal removed.	Transient—lasting 24 hours.....	+ +			
Obs. 30. Male, age 1 yr.	Feb. 22, 1914. Rt. adrenal and $\frac{3}{4}$ of left adrenal removed. Left lumbar vein ligated.	Transient—appearing $\frac{1}{2}$ hour af- ter op'n.	+ +			

TABLE III.

CARBOHYDRATE OBSERVATIONS ON DOGS WITH AN ADRENAL INSUFFICIENCY.

	Date.	Wgt.	Operation.	* Calculated tolerance (levulose, galactose).	Amt. given with stomach-tube.	Feh- ling's.	Nylan- der's.	Remarks.
Obs. 2. Male, age 6 mos.	Oct. 30, 1912	11 $\frac{3}{4}$ lbs.	Rem. 9/10 rt. adrenal.					
	Nov. 6, 1912	Rem. lft. adrenal.					
	Feb. 25, 1913	26.5 gm.	50 gm. levulose	—	—	
	Mar. 1, 1913	" "	70 " "	+	+	
	Mar. 2, 1913	" "	60 " "	+	+	
	Mar. 3, 1913	5.1 "	30 " galactose	+	+	
	Mar. 4, 1913	19 lbs.	" "	10 " "	—	+	
	Apr. 1, 1913	21 lbs.	32.6 "				
	Apr. 5, 1913	" "	50 gm. levulose	+		
	Apr. 7, 1913	" "	40 " "	+	+	
	Apr. 8, 1913	" "	30 " "	+	+	
	Apr. 11, 1913	21 lbs.	" "	20 " "	+	+	
	Apr. 12, 1913	6.5 "	7 " galactose	+	+	
	Apr. 27, 1913	Removal of piece (10 x 12 mm.) of remaining frag- ment, rt. adr.	+	+	Transient glycosuria begin- ning $\frac{1}{2}$ hr. after op'n.; convulsive seizures next A. M.
	Apr. 30, 1913	20 lbs.					
	May 29, 1913	31 gm.	25 gm. levulose	+	+	
	Jun. 9, 1913	" "	31 " "	—	+	
	Oct. 8, 1913	27 $\frac{1}{4}$ lbs.	42.4 "				
	Oct. 22, 1913	" "	43.5 gm. levulose	+	+	
	Oct. 23, 1913	" "	34.5 " "	+	+	
	Nov. 10, 1913	29 $\frac{3}{4}$ lbs.	Remaining hypertrophied fragment of rt. adrenal removed (cf. Figs. 5 and 6). Death 24 hrs. after.	Transient glycosuria.
Obs. 3. Male, age 1 yr.	Nov. 13, 1912	Rem. 9/10 rt. adrenal.					
	Nov. 20, 1912	Rem. entire left adrenal.					
	Mar. 1, 1913	49.8 gm.	60 gm. levulose	+	+	
	Mar. 3, 1913	" "	50 " "	—	—	
	Mar. 26, 1913	" "	70 " "	+	+	

TABLE III.—Continued.

	Date.	Wgt.	Operation.	* Calculated tolerance (levulose, galactose).	Amt. given with stomach-tube.	Feh-ling's.	Nylan-der's.	Remarks.
Obs. 3. Male, age 1 year.	Mar. 28, 1913	28½ lbs.	49.8 gm.	60 gm. levulose	+	+	
	Apr. 1, 1913	8.7 "	10 " galactose	+	+	
	Apr. 2, 1913	" "	5 " "	—	—	
	Apr. 6, 1913	27½ lbs.	Ether anæsthesia for ½ hr.; no. op.	8.5 "	—	—	
	Apr. 12, 1913	27 lbs.	8.1 "	9 gm. galactose	+	+	
	Apr. 19, 1913	48.3 "	37 " levulose	—	+	
	May 9, 1913	Ligation of vessels to remaining portion of rt. adrenal.	" "	+	+	Transient glycosuria appearing 1 hr. after operation; convulsive seizures.
	May 14, 1913	1/10 of remaining hypertrophied fragment on rt. removed. Death 24 hrs. later.	" "	+	+	Transient glycosuria.
Obs. 9. Female, age 1½ yrs.	Feb. 24, 1913	12½ lbs.	Rem. lft. adrenal. Rem. ¾ rt. adrenal.	+	+	Transient glycosuria for 24 hrs.
	Feb. 28, 1913	22.3 gm.	50 gm. levulose	+	+	
	Mar. 1, 1913	" "	40 " "	+	+	
	Mar. 2, 1913	" "	30 " "	+	+	
	Mar. 4, 1913	" "	10 " "	—	—	
	Apr. 1, 1913	" "	40 " "	+	+	
	Apr. 3, 1913	3.7 "	10 " galactose	—	—	
	Apr. 8, 1913	23.17 "	20 " levulose	—	—	
	Apr. 12, 1913	13 lbs.	3.9 "	5 " galactose	+	+	
	May 19, 1913	Removal of ¾ remaining hypertrophied fragment of rt. adrenal. Death 24 hrs. later.	+	+	Transient glycosuria on massaging adrenal before removal.

* Tolerance calculated after G. Quarta, Zeitschrift für Biol., V. 49, p. 522.

TOLERANZGRENZEN DER ZUCKERARTEN BEIM NORMALEN HUNDE PRO KG. KÖRPERGEWICHT.

Autoren.	Dextrose.	Lävulose.	Saccharose.	Laktose.	Galaktose.
F. Hoppe-Seyler: Virchows Archiv., 1856, Bd. 10 S. 144.....	—	—	20-30 3, 6 nur Lävulose ausgescheiden den.	—	—
Hofmeister: Archiv. f. exp. Path. u. Pharm., 1889, Bd. 25, S. 240..	1, 3-2, 5 2, 9-5, 8	—		0, 4-0, 8	—
W. Schlesinger: Wien. klin. Wehnschr., 1902, S. 30.....	10-11	—		—	—
R. Luzzatto: Archiv. f. exp. Path. u. Pharm., 1904, Bd. 25, S. 107..	—	—	—	1, 1	0, 06
Boeri und De Andreis: Policlin. V. Med., 1898, S. 477.....	4-6 (nüchtern) 10-13 (b. Ehrnahr.)	—	—	—	—
G. Quarta Zeitschrift für Biol., V. 49, p. 522....	Männliche Hunde	3, 20 5 3, 80 4, 25	2, 75 3, 05 — 3, 65	0, 80 2 1, 60 1, 75	— — — —
	Durchschnitt	4, 06	3, 11	1, 54	—
	Weibliche Hunde	10, 70 9, 15 11	3, 23 3, 50 4	2, 30 5, 90 3, 55	— — —
	Durchschnitt	10, 28	3, 58	3, 92	—

At autopsy, the remaining fragment of adrenal in this animal was found to contain a few medulla cells, but scarcely recognizable with the naked eye (Figs. 5 and 6, dog II). Microscopical examination showed that there was no hypertrophy nor other evidence of excessive activity of the medulla, a striking contrast in this respect to the cells of the three layers of the cortex.

It is apparent, then, that when the accelerating influence of the adrenals is removed, the inhibiting influence of the pancreas is counteracted by some of the other accelerators of glycogen mobilization.

V. TRANSPLANTATION OF THE ADRENALS.

In making transplants of the adrenals we have adhered to the principle emphasized by W. S. Halsted²¹ that an existing "physiological deficit" is one of the essentials to a successful "take."

We undertook these transplantation experiments with the hope that we might be able to determine:

- (1) Whether a fragment of cortex alone will "take" if transplanted into the kidney or the abdominal wall.
- (2) Whether such a graft will suffice to keep the animal alive after a total extirpation of both adrenals.

In regard to the first point, the microscopical examination of the graft has disclosed approximately normal-looking viable cells of the cortex in several instances. The majority of such grafts, however, undergo degenerative changes and are eventually replaced with scar tissue. Even when large fragments containing both cortex and medulla, are transplanted, the cortical cells may survive (Figs. 7 and 8, dog III), but the chromaffin elements entirely disappear.

We have made no attempt to transplant the entire gland by merely loosening it from its bed and maintaining the original blood-supply, although von Haberer²² has shown that grafts made in this way are often functional as well as microscopical "takes."

In order to prove the second point, it must be shown that the graft is of functional value. This test is made by removing the last remaining fragment of the original adrenal. Here again we have been unsuccessful, as is shown by Observation 3. In this animal (cf. table IV) about nine-tenths of the right adrenal was removed on Nov. 13, 1912, and a fragment of the portion removed was transplanted between the rectus and the peritoneum. One week later the entire left adrenal was extirpated. On May 9, 1913, about six months after the original operation, the larger vessels supplying the remaining fragment of the right adrenal were ligated; this operation was followed by convulsive seizures, subnormal temperature, loss of appetite and other symptoms of an acute adrenal insufficiency. The animal gradually recovered, however, and on May 14, 1913, about one-third of the remaining portion of the right adrenal

was removed. Again the symptoms of an adrenal insufficiency appeared and death ensued twenty-four hours later. The microscopical appearance of the portion of the adrenal removed on May 14 is shown in Fig. 1, dog III, plate I. There is a necrosis of almost the entire fascicular zone, apparently due to an interference with the blood supply, produced by the ligation of the vessels on May 9; the glomerular zone is greatly hypertrophied, but the cells of the medulla are approximately normal in appearance. The engrafted fragment is embedded in scar tissue, but is well vascularized (Figs. 7 and 8, dog III). The normal architecture has become distorted by the ingrowth of fibrous tissue and only isolated groups of adrenal cells are seen. These cells, however, all contain lipoids and are of the cortical rather than the chromaffin type. The specific stains for chromaffin tissue fail to disclose any cells of this type, so we must conclude that the medullary portion of the graft has been absorbed. This is possibly due to the fact that a sufficient degree of "physiological deficit," as far as the chromaffin system is concerned, is not produced by the partial extirpation of the adrenals. If this is true, it precludes the idea that the negative functional value of such a graft, as the one described above, is due to the fact that it contains no viable medullary cells. The only explanation we can offer for the failure of the above experiment is that the engrafted fragment of adrenal was deprived of its normal nerve supply. We have repeatedly had animals to survive and develop normally with but a minute fragment of one adrenal (no larger than the engrafted portion in Observation 3) remaining in its original bed. Such a fragment becomes embedded in fibrous tissue and acquires a collateral circulation as does a graft; it still retains or regains its nerve connections, however, since massage or partial extirpation of the gland, or stimulation of the sympathetic nerves in the neighborhood, will produce a transient glycosuria, while none of these manipulations on a graft are followed by a glycosuric response, provided all the adrenal tissue has been removed from its normal situation. On the other hand, v. Haberer has found that when an adrenal is mobilized so as to retain its normal blood-supply and is buried in the adjoining upper pole of the kidney, about fifty per cent of the animals will survive a total extirpation of the remaining adrenal; in other words, the adrenal thus transplanted to the kidney continues to function.

VI. THE POSSIBLE RELATION BETWEEN THE SUPRARENAL BODIES, THE THYMUS, AND THE LYMPHATIC SYSTEM.

An interesting combination of status thymico-lymphaticus in association with changes in other organs is seen in Addison's disease. Even in the older literature on Addison's disease²³ a local or general hyperplasia of the lymphatic system is frequently noted in the autopsy reports. Most often it is the mesenteric and retroperitoneal glands and the lymph follicles in the walls of the intestines that are swollen, while those in the neck, axillæ and groins show but little change.

²¹ Halsted, W. S.: The Transplantation of Parathyroid Glands in Dogs. *Proceedings of the Soc. for Exper. Biol. and Med.*, 1908, v, 74-77.

²² v. Haberer: Experimentelle Verlagerung der Nebenniere in die Niere. *Archiv. f. klin. Chir.*, 1908, LXXXVI, 399.

²³ Averbek. *Die Addisonische Krankheit*. Erlangen, 1869.

On the other hand, it was noted by Wiesel,²⁴ in 1904, that many of the individuals coming to autopsy with status thymico-lymphaticus have a striking hypoplasia of the chromaffin system. These observations were confirmed by v. Neusser,²⁵ Bittorf,²⁶ and others. Hedinger²⁷ has studied a large number of cases with this point in mind and comes to the conclusion that status thymicus and status lymphaticus are entirely different conditions. In the former, the chromaffin system is usually normal in appearance and amount, but there are hypertrophic changes in the cortex of the adrenals; while in status lymphaticus degenerative or atrophic changes are frequently found in the medulla of the adrenal with but little or no change in the cortex.²⁸

The only references we have seen to any experimental observations concerning the relation between the adrenals and the lymphatic system is the brief article published in 1899 by Auld,²⁹ and the reference made by Schaefer³⁰ in the Oliver-Sharpey lectures, in 1908, concerning the effects of extirpation of the spleen and adrenals in rats. Auld made a partial extirpation of the adrenal bodies in four dogs and states in his conclusions that in all four animals two phenomena were very apparent: (1) a great hypertrophy of the thymus; (2) a considerable enlargement of the spleen. There is no mention of changes in the lymph-glands, but he infers from his experiences that thymus feeding would possibly be of value in Addison's disease. Schaefer removed the spleen and adrenals in rats one month of age. Subsequent growth was normal; the animals were sacrificed four months later. There was no pigmentation, but a marked hyperplasia of the lymph glands.

Our attention was first directed to the possible relation between the adrenals and the lymphatic system by the autopsy findings in Observation 2. An adrenal insufficiency was established in this animal (cf. table IV) by removing at four different operations all but a minute fragment at the upper pole of one adrenal. For several days after the third operation the animal was in a semi-comatose condition and had frequent convulsive attacks; recovery gradually ensued, however, and during the succeeding eight months growth, development and sexual functions were apparently normal (Fig. 9, dog II).

Death followed within a few hours after the removal of the remaining fragment of adrenal, demonstrating conclusively that this gland is necessary to life. The most striking feature at the autopsy was the large mesenteric, retroperitoneal, and mediastinal lymph glands, together with an atrophic thymus. Microscopical examination of the enlarged lymph glands show small, atrophic-looking lymph cords, but a very marked hyperplasia of the endothelial cells lining the lymph sinuses and of the large mononuclear cells in the germinal centers. These endothelial cells show but little evidence of phagocytosis and there is no increase in the number of leucocytes or eosinophilic elements. There was no evidence of a chronic infection; no skin eruption, and not an abnormal number of intestinal parasites.

The autopsy on Observation 3 also revealed a general enlargement of the lymph glands and, in addition, a persistent thymus. This was a full-grown adult, approximately one and a half years of age. Portions of the adrenal were removed at three different operations; and here again convulsive seizures, drowsiness—almost amounting to coma—and a scanty secretion of urine, all symptoms of an adrenal insufficiency, were present. At the third operation the large vessels supplying the remaining fragment of adrenal were ligated, leading to a necrosis of the fascicular zone of the cortex with no evident injury to the medulla (Fig. 1, dog III, plate I).

There was a general enlargement of the lymph glands, but the changes were most marked in those of the mesentery and retroperitoneal region. Microscopically, the germinal centers are prominent and filled with large mononuclears; the lymph cords are packed with small mononuclear cells; the endothelial cells lining the lymph sinuses are more abundant than in similar glands from control animals, but much less numerous than in Observation 2. The thymus is rich in small mononuclears, while the endothelial cells and Hassal's corpuscles are much less conspicuous than in control glands from animals of approximately the same age. The eosinophilic cells are more numerous than normal, and, for the most part, lying just outside the large blood vessels.

In Observation 20 the animal was about 18 months of age and the adrenal insufficiency was of four and a half months' duration. During this period there was a gain of five and a half pounds in weight, and the skeletal development and the sexual activities were apparently normal. The animal was accidentally killed. The autopsy revealed:

(1) A large vascular thymus, measuring 14 x 6 x 2.5 cm. It is packed with lymphocytes and has numerous large, well-preserved Hassal's bodies.

(2) Large mesenteric, retroperitoneal and mediastinal lymph glands.

(3) The inguinal and axillary glands show no marked increase in size, but are deeply pigmented. The pigment is contained in the endothelial cells lining the lymph sinuses.

(4) The lymph follicles in the lower portion of the small intestine are large and prominent, and microscopically, are seen to be composed almost entirely of large mononuclear or

²⁴ Wiesel. Zur Pathologie des chromaffinen Systemes. Virchows Archiv., 1904, CLXXVI, 103-114.

²⁵ Neusser u. Wiesel. Die Erkrankungen der Nebennieren. Wien, 1910.

²⁶ Bittorf: Die Pathologie der Nebennieren und des Morbus Addisonii. Jena, 1908.

²⁷ Hedinger: Keimzentrenbildung im Knochenmark des Oberschenkels bei Status Lymphaticus. Verhandl. d. med. Gesellsch. Basel. Sitzung, XXXI, Okt., 1907. Ueber Beziehungen Zwischen Status Lymphaticus und Morbus Addisonii, Verhandl. d. Deutsch. Path. Gesellsch. Dresden, 1907, p. 29.

²⁸ Wiesel: Pathologie des Thymus. Ergebnisse der Alg. Pathologie, 1911, XV, 416-728.

²⁹ Auld: Additional Observations on the Function of the Suprarenal Gland. Brit. Med. Jour., 1899, I, 1327.

³⁰ Schaefer: Oliver-Sharpey Lectures on the Present Condition of our Knowledge Regarding the Function of the Suprarenal Capsule. Brit. Med. Jour., 1908, I, 1277-1281 and 1346-1351.

TABLE IV.

NOTES ON THE MICROSCOPICAL APPEARANCE OF THE LYMPHATIC SYSTEM AND DUCTLESS GLANDS IN THE OBSERVATIONS MENTIONED IN THIS PAPER.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 2. Male, age 6 mos.	Oct. 30, 1912. 11 $\frac{3}{4}$ lbs. Mar. 5, 1913. 19 lbs. Apr. 1, 1913. 21 lbs. Apr. 11, 1913. 21 $\frac{1}{4}$ lbs. Apr. 30, 1913. 20 lbs. Oct. 8, 1913. 27 $\frac{1}{4}$ lbs. Nov. 10, 1913. 29 $\frac{3}{4}$ lbs.	Oct. 30, 1912. Removal of 9/10 rt. adrenal. Fragment transplanted between peritoneum and rectus muscle. Nov. 6, 1912. Removal of entire left adrenal. Transplanted between peritoneum and rectus muscle. Apr. 27, 1913. Portion (10 x 12 m.m.) of the remaining rt. adrenal removed. May 15, 1913. Removal of area of transplants in abdominal wall; found to be replaced by scar tissue. Nov. 10, 1913. Removal remaining fragment of rt. adrenal.	One year and 10 days.... Death 18 hours after removal of last remaining fragment of right adrenal.	Animal well nourished. No remains of adrenal tissue; no accessory adrenals found. Most striking change is the <i>general enlargement of the lymph glands</i> . Testicles large. Other organs show no gross abnormality. <i>Microscopical.</i> (1) <i>Adrenal</i> (removed Oct. 30, 1912): Normal appearance and lipid distribution. (2) <i>Adrenal</i> (removed Nov. 6, 1912): Beginning hypertrophy as shown by the increase in size and in lipid content of the cells of the zona glomerulosa. No evident change in other zones of cortex nor in medulla. (3) <i>Adrenal</i> (removed Apr. 27, 1913): Marked hypertrophy of all zones of cortex; medulla small; cells show no evidence of hypertrophy. Lipoids most abundant in zona fasciculata; connected in large irregular globules in other two zones of cortex. (4) <i>Adrenal</i> (removed Nov. 10, 1913) (cf. Figs. 3 and 4): Large blood sinus in medulla; but very few medullary cells, and these show no hypertrophic changes. Hypertrophy chiefly in zona fasciculata. Lipoids abundant, but in large clumps—both intracellular and extracellular. <i>Thyroid</i> : Normal; cells enboidal; no diminution in the amount of colloid. <i>Parathyroid</i> : Possibly shows hypertrophic changes (?). <i>Hypophysis</i> : Numerous colloidal bodies in posterior lobe and stalk; otherwise normal. <i>Testicle</i> : Abundant, normal-looking spermatozoa. No change in interstitial cells. <i>Pancreas</i> : Islets very vascular and unusually prominent—probably a definite hyperplasia. <i>Spleen</i> : Large Malpighian bodies due to hyperplasia of the endothelial (?) cells; but few lymphocytes. <i>Lymph Glands</i> : The lymph sinuses are packed with large endothelial cells containing pigment. The medullary cords are atrophic; but few lymphocytes surround the large germinal centers. <i>Thymus</i> : Was lost. <i>Transplant</i> : Replaced with scar tissue. No recognizable adrenal cells.
Obs. 3. Male, age 1 year.	Nov. 13, 1912. 22 lbs. Mar. 30, 1913. 28 $\frac{1}{2}$ lbs. Apr. 6, 1913. 27 $\frac{1}{2}$ lbs. Apr. 11, 1913. 27 lbs.	Nov. 13, 1912. Removal of 9/10 rt. adrenal. Fragment transplanted between peritoneum and rectus muscle. Nov. 20, 1913. Removal of entire left adrenal. No transplant. May 9, 1913. Ligation of larger vessels supplying remaining fragment of right adrenal. Had convulsive seizures for several days following this operation. May 14, 1913. Removal of minute fragment of rt. adrenal.	Six months Death 24 hrs. later. Transplant of no functional value.	Animal well nourished. No accessory adrenals found. The transplant in abdominal wall is easily recognizable; can be seen shimmering through the peritoneum. Most striking is the <i>general enlargement of the lymph-glands</i> . The spleen is also enlarged. The thymus is large and vascular. Other organs show no gross changes. <i>Microscopical.</i> <i>Adrenal</i> (removed at autopsy, May 15): Necrosis of zona fasciculata; hypertrophy of the zona glomerulosa; approximately normal looking zona reticularis and medulla (cf. dog 3, plate I). <i>Pancreas</i> : Numerous prominent islets; vessels congested. <i>Spleen</i> : Hyperplasia of endothelial (?) cells in the germinal center of the Malpighian corpuscles; but few lymphocytes; many giant cells in pulp. <i>Hypophysis</i> : No increase in number of colloid bodies in posterior lobe, as in Obs. 2. <i>Liver</i> : Normal in appearance. <i>Thymus</i> : Vessels engorged with blood. <i>Hyperplasia of lymphocytes</i> ; only small islands of medulla to be seen; Hassal's bodies are present, but not numerous. The thymus of this dog (1 $\frac{1}{2}$ yrs. of age) looks much like that of a normal puppy. <i>Lymph glands</i> : Great proliferation of the endothelial (?) cells in the center of the germinal center, with an increased number of lymphocytes; the very picture of a status lymphaticus clinically. <i>Transplant</i> (cf. Figs. 5 and 6): Large clumps of lipid containing cells (evidently cortex cells) embedded in fibrous tissue. Well vascularized. Specific chromaffin stains show that none of the medulla cells have survived. (There are numerous well-preserved cells of the cortex of the adrenal, but they proved to be of no functional value.

TABLE IV.—Continued.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 4. Male, age 6 mos.	Jan. 24, 1913. 10-1/5 lbs.	Jan. 24, 1913. Removal entire right adrenal. No transplant. Feb. 3, 1913. Removal of 9/10 left adrenal, leaving part of upper pole. Transplant under peritoneum.	17 days For a week preceding death (Feb. 10), had a subnormal temperature, tremors, drowsiness, etc.	Has rapidly lost weight since last operation. No cause found for death aside from adrenal insufficiency. <i>Microscopical.</i> (1) <i>Adrenal</i> (removed Jan. 24): normal. (2) <i>Adrenal</i> (removed Feb. 3): beginning hypertrophy as evidenced by an increase in size of the zona glomerulosa. In the middle and inner zone of the cortex the lipoids are more abundant than in control gland (Jan. 24). Cells of the medulla changed in appearance. <i>Pancreas</i> : Islets prominent and vessels engorged with blood. <i>Hypophysis</i> : Possibly an increase in eosinophilic cells in the anterior lobe; no change in posterior lobe. <i>Spleen</i> : No striking change. <i>Thyroid</i> : Normal. <i>Testicle</i> : Large numbers of interstitial cells, perhaps normal for an animal of this age. No spermatozoa seen. <i>Thymus</i> : Vessels engorged with blood. Composed chiefly of lymphocytes. But few Hassal's bodies to be seen; only small islands of medulla. This gland is probably undergoing acute hyperplastic changes; the histological appearance is similar to that of a normal puppy 10 days of age. <i>Transplant</i> : Round cell infiltration. Adrenal cells scarcely recognizable; numerous cholesterol crystals.
Obs. 5. Female, age 6 mos.	Feb. 5, 1913. Removal of both adrenals. No transplant.	8 days First symptoms of adrenal insufficiency appeared 5 days after operation (drowsiness, loss of appetite, subnormal temperature, muscular weakness).	No evident cause for death aside from adrenal insufficiency. No accessory adrenal tissue was found after a careful search. <i>Microscopical.</i> <i>Hypophysis</i> : A marked diminution in the number of eosinophilic cells in the anterior lobe; posterior lobe looks normal. <i>Ovary</i> : Looks normal. <i>Thymus</i> : Vessels engorged with blood. Hassal's bodies numerous and undergoing degenerative changes. Great predominance of lymphocytes. Approximately normal for an animal of this age. <i>Pancreas</i> : } <i>Thyroid</i> : } Normal <i>Liver</i> : }
Obs. 6. Female, age 2 years.	Feb. 10, 1913. 7 lbs.	Feb. 10, 1913. Removal of both adrenals. Transplant under peritoneum.	24 hours	No evident cause for death aside from the absence of both adrenals; no accessory adrenals found. <i>Microscopical.</i> <i>Thymus</i> : Vessels engorged with blood; large areas of hemorrhage. Otherwise only regressive changes are seen, probably due to the age of the animal.
Obs. 8. Male, age 2 yrs.	Feb. 19, 1913. 14 1/2 lbs.	Feb. 19, 1913. Removal of entire rt. adrenal. Transplant under peritoneum.	One month. Animal had "distemper" for several weeks and a terminal acute bronchial pneumonia. Convulsive seizures for several days preceding death.	Chronic infection of upper respiratory passages and a bronchial pneumonia. (1) <i>Adrenal</i> removed at operation Feb. 19, measures 3 x .6 x .5 cm. (2) <i>Adrenal</i> removed at autopsy Nov. 19, measures 3.5 x .9 x .7 cm. <i>Liver</i> : shows cloudy swelling and focal necrosis. <i>Microscopical.</i> (1) <i>Adrenal</i> (removed Feb. 19): normal. (2) <i>Adrenal</i> (removed May 19) (cf. dog 8, plate I): Hypertrophy due to a multiplication of cells in the zona fasciculata; there is a very striking <i>interstitial fibrosis</i> in this zone, and <i>areas of focal necrosis</i> . The lipoids have almost entirely disappeared from the two inner zones of the cortex, but abnormally abundant in the glomerular zone. <i>Liver</i> : Areas of focal necrosis. <i>Thyroid</i> : Many of the alveoli filled with large desquamated epithelial cells; the colloid is scanty in amount and vacuolated. <i>Testicle</i> : Looks normal. <i>Spleen</i> : Hyperplasia Malpighian bodies. <i>Transplant</i> : Cortical cells still recognizable; cholesterol crystals.

TABLE IV.—Continued.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 9. Pregnant female, age 2 years. Two normal puppies born March 31.	Feb. 24, 1913. 12½ lbs. Apr. 11, 1913. 13 lbs.	Feb. 24, 1913. Removal of entire left adrenal and ⅔ of right. Transplant under peritoneum. May 19, 1913. Removal of ¾ remaining fragment of right adrenal. Transplant into upper pole of kidney.	Two months and 25 days. Death 24 hours after last operation.	Well nourished. No cause for death found other than adrenal insufficiency. Ovaries show large areas of luteum cells. <i>Microscopical.</i> <i>Adrenal:</i> Most striking is the absence of <i>hypertrophic change</i> in the portion of right adrenal removed at operation on May 19. There is also no variation from the normal in the amount and distribution of lipoids. <i>Ovary</i> (examined 7 wks. after birth of puppies): The greater part of both ovaries is composed of luteum cells. <i>Pancreas:</i> Islets large; vessels engorged with blood. <i>Lymph glands:</i> { No tissue removed at autopsy. <i>Thymus:</i> {
Obs. 11. Female, age 1½ years.	Mar. 31, 1913. 36 lbs. Apr. 11, 1913. 32 lbs.	Mar. 31, 1913. Removal of entire left adrenal. Transplant under peritoneum.	14 days	Death due to pneumonia. Most striking is the large <i>persistent thymus</i> and a <i>general enlargement of the lymph glands</i> . The right adrenal is almost twice the normal size. <i>Microscopical.</i> (1) <i>Adrenal</i> (removed at operation) (cf. dog II, plate I): Normal control. (2) <i>Adrenal</i> (autopsy) (cf. dog II, plate I): Hypertrophy of zona fasciculata; the other zones of cortex are also enlarged. The cells of the medulla are swollen; their nuclei larger and contain chromatin masses. The lipoids have all practically disappeared from the reticularis zone; are scanty in the fascicularis, but abundant in the glomerulosa. <i>Thyroid:</i> Many alveoli filled with desquamated epithelium; colloid vacuolated. <i>Hypophysis:</i> Great excess of the hyaline bodies of Herring in posterior lobe; the eosinophilic cells of the anterior lobe are small and inconspicuous, the predominating cells non-granular with a large vesicular nucleus (due to previous pregnancy?). <i>Parathyroid:</i> Vessels engorged. <i>Ovary:</i> Normal. <i>Transplant:</i> Round cell infiltration; fatty degeneration. <i>Liver:</i> Focal necrosis around portal spaces. <i>Thymus:</i> Animal had a general infection.
Obs. 12. Female, age 6 mos.	Apr. 6, 1913. 20½ lbs. Apr. 11, 1913. 20 lbs.	Apr. 6, 1913. Removal of entire left adrenal.	One month and 19 days. Sacrificed on account of distemper.	Has rapidly lost weight during the past 2 weeks, due to a chronic infection of the upper air-passages. The rt. adrenal is hypertrophied. <i>Microscopical.</i> (1) <i>Adrenal</i> (removed at operation): Normal control. (2) <i>Adrenal</i> (autopsy): Hypertrophy due to multiplication of cells in the zona fasciculata; to a less extent in the other 2 zones of the cortex. Medulla is hyperæmic and vessels engorged with blood. Lipoids more abundant than normal in the zona glomerulosa; scanty in other cortical zones. No focal necroses nor fibrosis in cortex as in Obs. 8. <i>Thymus:</i> { Animal had a long standing chronic infection; <i>Lymph Glands:</i> { lymph glands are pigmented.
Obs. 13. Male, age 6 mos.	Apr. 13, 1913. 9¾ lbs.	Apr. 13, 1913. Removal of entire left adrenal. May 18, 1913. Removal of entire rt. adrenal.	One month and 5 days. Death 24 hours after last operation.	No cause for death found aside from adrenal insufficiency. Large thymus and hyperplasia of the mesenteric lymph glands; those in neck and groin not enlarged. <i>Microscopical.</i> (1) <i>Adrenal</i> (removed Apr. 13): Normal control. (2) <i>Adrenal</i> (removed May 18): No <i>hypertrophy</i> and no change in amount and distribution of lipoids. No change seen in the medulla. (Cause.) <i>Thymus:</i> The large endothelial cells are especially conspicuous; these cells show no evidence of phagocytosis. But few Hassall's bodies to be seen. No increase in the number of lymphocytes in the cortex. The size of the gland is apparently due largely to an hyperplasia of the endothelial cells in the medulla. <i>Lymph Glands:</i> Large germinal centers; but few lymphocytes. Hyperplasia of endothelial cells lining lymph sinuses. <i>Thyroid:</i> Normal.

TABLE IV.—Continued.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 14. Female, age 6 mos.	Apr. 20, 1913. 12¼ lbs. Apr. 30, 1913. 12 lbs.	Apr. 20, 1913. Removal of entire left adrenal. No transplant. Apr. 27, 1913. Removal of ⅔ rt. adrenal. May 4, 1913. Removal of remainder of rt. adrenal.	14 days Death 24 hours after 3d operation.	About 30 cc. of hemorrhagic fluid in the left pleural cavity, and early stage of bronchial pneumonia in lower lobe of left lung. No evidence of infection in the peritoneal cavity. No adrenal tissue left; no accessory adrenal bodies found. Mesenteric lymph glands seem larger than normal. <i>Microscopical.</i> <i>Thymus:</i> Very striking hyperæmia. The most marked change is the predominance of the cortex; there is but little medulla. Hassall's bodies degenerated. Many large mononuclear cells in the interlobular tissue and around the blood-vessels. (There is no control for this observation.) <i>Spleen:</i> Large amount of pigment in giant cells and endothelial cells of pulp; the Malpighian corpuscles are possibly larger than normal. <i>Thyroid:</i> Looks normal. <i>Adrenal (removed May 4):</i> No striking hypertrophy; lipoids are abundant in all three zones of cortex, and collected in large clumps.
Obs. 15. Male, age 6 mos.	May 4, 1913. 18½ lbs.	May 4, 1913. Partial removal of rt. adrenal, leaving about ⅓ at lower pole. Removal of entire left adrenal. Transplant fragment in kidney. May 25, 1913. Remaining fragment of rt. adrenal removed. Had doubled in size by actual measurement.	25 days Animal succumbed on 4th day after operation.	No accessory adrenal tissue found. No evidence of infection. Has strikingly large thymus. Animal has rapidly lost weight since last operation. <i>Microscopical.</i> (1) <i>Adrenal (removed May 4):</i> Normal control. (2) <i>Adrenal (removed May 25):</i> Contains both cortex and medulla. Cortex greatly hypertrophied, largely due to increase in size of zona fasciculata. Medulla shows no hyperplasia either grossly or microscopically. There is an extensive fibrosis and round cell infiltration of the cortex; no such changes in the medulla. <i>Thyroid:</i> <i>Liver:</i> <i>Spleen:</i> <i>Testis:</i> } Show no marked change. <i>Thymus:</i> Lost. <i>Transplant (Kidney):</i> Adrenal cells viable around periphery; necrosis, round cell infiltration and cholesterol crystals in the central portion; of no functional value.
Obs. 17. Male, age —.	No record.	May 12, 1913. Removed entire rt. and ⅔ left adrenal. Transplant in kidney. May 30, 1913. Removal of remainder of left adrenal.	18 days Death 18 hours after last operation.	No infection. No accessory adrenal tissue found. All of the adrenal had been removed on both sides. <i>Microscopical.</i> (1) <i>Adrenal (removed May 12):</i> Normal control. (2) <i>Adrenal (removed May 30):</i> hypertrophy not so great as in Obs. 15. Increase in size of zona fasciculata; no change seen in the medulla. Lipoids are more abundant than normal in zona glomerulosa; scanty in the other 2 zones of cortex in contrast to Obs. 15. <i>Transplant:</i> Scarcely recognizable; cholesterol crystals in central portion; a few viable cells around periphery; of no functional value.
Obs. 20. Male, age 1½ yrs.	Nov. 20, 1913. 18½ lbs. Dec. 7, 1913. 18½ lbs. Feb. 22, 1914. 24 lbs.	Nov. 23, 1913. Removal of entire rt. adrenal. Transplant in kidney. Dec. 7, 1913. Removal 9/10 left adrenal, leaving fragment at upper pole. Ligation of adrenal vein on left. Transplant in kidney. Mar. 1, 1914. Accidentally killed.	3 months and 7 days.....	Well nourished. Mesenteric and retroperitoneal lymph glands much enlarged; those in neck, axillæ and groin are much enlarged and deeply pigmented. Remaining fragment of left adrenal much hypertrophied. No accessory adrenal found. Spleen not markedly enlarged, but the Malpighian bodies are very prominent. Pancreas, liver, heart and aorta look normal. Thyroid not enlarged. Stomach shows no evidence of ulcer. Intestines: Payer's patches from 2 to 3 cm. in diameter and very prominent. A few pin-worms in small intestine, but otherwise normal. Bone-marrow looks normal. The epiphyses of the long bones and ribs look normal. There is an extremely large thymus, measuring 14 x 6 x 2.5 cm.; the lower lobe extends down to the level of the apex of the heart. The tonsils are much enlarged, almost meeting in mid-line. <i>Microscopical.</i> <i>Thymus:</i> Hyperplasia of the lymphocytes (or small mononuclear elements). Only small areas of medulla. Hassall's bodies are numerous, large and well preserved. No increase in eosinophilic cells. <i>Lymph Gland (mesentery):</i> Large germinal centers filled with large mononuclear cells; no marked hyperplasia of the lymphocytes. Increase in size and number of endothelial cells lining lymph sinuses, many of which are loaded with pigment. Other lymph glands show endothelial hyperplasia and pigmentation. <i>Spleen:</i> Hyperplasia of large mononuclear cells in Malpighian bodies. Giant cells filled with pigment and many large endothelial cells in pulp. (1) <i>Adrenal (removed Nov. 23):</i> Normal control. (2) <i>Adrenal (removed Dec. 7):</i> Shows some evidence of hyper-activity and hyperplasia of the cells of the medulla. Hypertrophy of zona fasciculata of cortex. Lipoids scanty, but in all 3 zones of the cortex particularly abundant in the zona glomerulosa. (3) <i>Adrenal (removed at autopsy):</i> Cells of medulla normal in size and appearance, in contrast to specimen of Dec. 7. Very marked hypertrophy in zona fasciculata. Lipoids have almost entirely disappeared from inner 2 layers of cortex, but very abundant in outer zone. <i>Thyroid:</i> Vesicles filled with colloid; cells normal. <i>Liver:</i> Looks normal (but not stained for glycogen). <i>Tonsil:</i> Composed almost entirely of large mononuclear cells. <i>Testis:</i> Numerous spermatozoa; no change in size and number of interstitial cells. <i>Solitary Follicles</i> in intestine composed almost entirely of large mononuclear cells like those in germinal centers of lymph glands. But very few lymphocytes to be seen. <i>Pancreas:</i> Islets large and vessels engorged with blood.

TABLE IV.—Continued.

Case No.	Weight.	Operations.	Duration of life.	Post-mortem conditions.
Obs. 22. Female, age 3 mos.	Nov. 30, 1913. 7¼ lbs.	Nov. 30, 1913. Removal of entire left adrenal. Ligation rt. adrenal vein. Transplant in kidney. Dec. 14, 1913. Removal of rt. adrenal, leaving approximately 1/10 at upper pole.	15 days Death 24 hours after last operation.	No infection of the respiratory tract or peritoneal cavity. Animal well nourished. Lymph glands not strikingly enlarged. Lungs, heart, liver, kidneys and intestines all look normal. Thymus atrophic. No ulcers in stomach. <i>Microscopical.</i> (1) <i>Adrenal</i> (removed Mar. 30): Normal control. (2) <i>Adrenal</i> (removed Dec. 14): Medulla cells look normal. Fibrosis and round cell infiltration in mid-zone of the cortex. Hypertrophy of cells of zona glomerulosa (much the same appearance as in dog 3). Lipoids abundant in outer zone; scanty in other zones of cortex. (3) <i>Adrenal</i> (removed at autopsy): Undergoing disintegration; apparently entire blood-supply has been cut off. <i>Thymus</i> : Undergoing regressive changes; but few lymphocytes. Hassal's bodies not numerous and degenerating. <i>Lymph Glands</i> : Large germinal centers; hyperplasia endothelial cells lining lymph sinuses. <i>Transplant</i> : Complete degeneration of medulla cells; mid-zone of cortex contains approximately normal-looking cells. <i>Thyroid</i> : Normal. <i>Ovary</i> : Normal.
Obs. 23. Male, age 3 mos.	Nov. 30, 1913. 7 lbs.	Nov. 30, 1913. Removal of entire right adrenal. Ligation of left adrenal vein. Transplant in kidney. Dec. 14, 1913. Removal of left adrenal, leaving approximately 1/10 at upper pole.	24 days The animal survived 10 days with but a small fragment of cortex; no medulla found at autopsy. Had marked symptoms of adrenal insufficiency for 8 days preceding death.	Death apparently due to some infection of the gastro-intestinal tract; m. m. of stomach and entire small intestine is inflamed, oedematous and covered with mucus; no gastric ulcers. General enlargement of lymph glands. Thymus about normal for animal of this age—a striking contrast to Obs. 22. <i>Microscopical.</i> <i>Adrenals</i> : Approximately the same changes as described in Obs. 22—with the exception that the remaining fragment at autopsy contained no medulla cells. <i>Thymus</i> : many lymphocytes (in general is about normal for this age). <i>Lymph Gland</i> : Marked hyperplasia of germinal centers and endothelial cells lining lymph sinuses. No increase in leucocytes nor other evidence of general infection. <i>Transplant</i> : Complete degeneration. <i>Liver</i> : Normal. <i>Hypophysis</i> : Normal; no increase in hyaline bodies in posterior lobe.
Obs. 24. Female, age 3 mos.	Dec. 8, 1913. 9¾ lbs. Dec. 16, 1913. 9 lbs.	Dec. 8, 1913. Removal of entire right adrenal and all but 1/20 of left adrenal. Ligation of left adrenal vein.	10 days	There is a marked gastro-enteritis; the m. m. of stomach, small intestine, and colon is swollen and injected; no ulcerations seen. The m. m. of the oesophagus is not involved. <i>Microscopical.</i> <i>Adrenal</i> (removed at autopsy): Hypertrophy of the fascicular zone; almost complete disappearance of lipoids in all the zones of the cortex. Remaining medulla microscopical in size; medulla cells show no evidence of hypertrophy. <i>Lymph Glands</i> (animal had gastro-enteritis): Hyperplasia of endothelial cells lining lymph sinuses; lymphocytes not changed; no abnormal number of leucocytes. <i>Spleen</i> : Hemorrhages in pulp, also areas of focal necrosis; very marked proliferation of endothelial cells. Some Malpighian bodies contain no lymphocytes, only large endothelial cells.
Obs. 25. Female, age 6 mos.	Feb. 1, 1914. No record.	Feb. 1, 1914. Removal of entire left adrenal and ¾ of right. (The right adrenal was cut longitudinally.)	5 days	Since operation has gradually become more listless each day; temperature subnormal; appetite poor; marked muscular weakness. <i>Microscopical.</i> <i>Adrenal</i> (removed at autopsy): Undergoing degenerative change; apparently much of the blood supply was cut off at operation. <i>Lymph Glands</i> (mesenteric): Lymph sinuses filled with large endothelial cells; they show active phagocytosis of blood pigment. No hyperplasia of the germinal centers. <i>Other Organs</i> are approximately normal.
Obs. 26. Male, age 3 mos.	No record.	Feb. 1, 1914. Removal of entire left adrenal and ¾ of right. (The right adrenal was cut transversely, leaving the upper pole.) Adrenal vein on right not ligated.	24 hours	No cause for death found aside from an adrenal insufficiency. <i>Microscopical.</i> <i>Adrenal</i> (removed at autopsy): Has a good blood-supply; cells of cortex and medulla are well preserved.
Obs. 29. Male, age 1 year.	Feb. 22, 1914. 13½ lbs.	Feb. 22, 1914. Removal of entire right adrenal, and ¾ of left. Mesenteric lymph gland removed for control. Transplant in abdominal wall.	17 days	Sacrificed on Mar. 10. The remaining portion of adrenal is hypertrophied. Abscess prostate; otherwise, organs look normal. <i>Microscopical.</i> <i>Adrenal</i> (removed at autopsy): Hypertrophy, chiefly the fascicular zone. Lipoids most abundant in reticular zone, the opposite to that seen in physiological hypertrophy uncomplicated by infection. <i>Lymph Glands</i> : Contain many leucocytes; otherwise no marked change from normal.
Obs. 30. Male, age 1 year.	Feb. 23, 1914. 16 lbs.	Feb. 22, 1914. Removal entire left adrenal and ¾ of rt.	48 hours	Hemorrhage into medulla of remaining fragment of adrenal. Refer to protocol in text. <i>Microscopical.</i> <i>Thymus</i> : Marked congestion and edema of entire gland; otherwise normal. <i>Adrenal</i> (removed at autopsy): Aside from hemorrhage, the gland is approximately normal in appearance. No change in lipoids.
Obs. 31. Male, age 4 mos.	No record.	Feb. 23, 1914. Removal entire left adrenal and ¾ of rt.	24 hours	No cause for death found aside from adrenal insufficiency. <i>Microscopical.</i> <i>Adrenal</i> (removed at autopsy): Beginning disintegration of the cells of both cortex and medulla, apparently due to insufficient blood-supply.

endothelial cells, similar to those in the germinal centers of the lymph glands.

(5) The spleen is slightly larger than normal and the Malpighian bodies stand out with great distinctness. The pulp contains numerous giant cells and endothelial cells filled with pigment. The center of the Malpighian bodies is filled with cells similar to those in the germinal centers of the lymph glands and in the solitary follicles of the small intestine. The lymphocytes are also more abundant than normal.

(6) The tonsils are much larger than in control animals of approximately the same age, and are made up of endothelial-like reticular cells with fragmented nuclei, but contain very few lymphocytes.

(7) The remainder of the ductless glands show no gross abnormality.

The increase in size of the lymph glands is apparently due to an hyperplasia of the cells lining the medullary sinuses and in the germinal centers. There is certainly no increase in number of the lymphocytes.

Similar observations were made on several other animals with a long-standing adrenal insufficiency. In order to make sure, however, that these changes in the lymph glands are really brought about by the partial extirpation of the adrenals, we have prepared a series of animals which are to be kept under observation for at least a year. In each of these animals as much of the adrenal was removed as is compatible with life. At the time of the operation, a mesenteric lymph gland was also extirpated as a control. Frequent observations will be made on the general blood picture and the changes in the lymphatic system. The results we hope to present in a subsequent communication.

CONCLUSIONS.

(1) In the dog, the suprarenal glands are vital organs, and it is probably the cortex rather than the medullary portion which is essential to life.

(2) After a partial extirpation of the adrenal, the remaining portion undergoes hypertrophic changes. The increase in size is due to a multiplication and enlargement of the cells of the cortex, chiefly in the fascicular zone; the medulla shows no hypertrophic changes, either grossly or microscopically.

(3) A chronic infection in an animal with an adrenal insufficiency is occasionally associated with an interstitial fibrosis and destruction of the cells of the fascicular zone of the cortex. An acute general infection in an animal with an adrenal insufficiency produces in some instances focal areas of complete cell destruction (without hemorrhage) in the fascicular zone of the cortex of the remaining portion of the adrenal. In no instance have we seen hemorrhages or injury to the cells of the medulla of the adrenal resulting from an acute or chronic infection in the dog.

(4) After an "almost total" removal of both adrenals, the animals often have general convulsive seizures, a subnormal

temperature and other symptoms of an acute adrenal insufficiency; in some instances, recovery gradually ensues after such symptoms and the animal subsequently develops in a normal manner as regards growth and sexual functions. There is also no change in disposition. They increase in weight, but not to an abnormal extent. There is no polyuria.

(5) There is no permanent raising or lowering of the carbohydrate tolerance resulting from an adrenal insufficiency.

(6) A transient glycosuria follows the operative manipulation of either the right or the left adrenal.

(7) An autoplasmic transplantation of a fragment of adrenal may "take," but is of no functional value. When a fragment of adrenal containing both cortex and medulla is transplanted, the cortical cells may survive, but the medullary cells are absorbed.

(8) There seems to be a definite relationship between the suprarenal glands and the lymphatic system. The most striking feature at autopsy on an animal with a long-standing adrenal insufficiency is the enlargement of the mesenteric and retroperitoneal lymph glands and the solitary lymph follicles in the walls of the intestine. Not infrequently there is also an hyperplasia of the thymus.

Further observations are being made to confirm these findings.

We wish to acknowledge the assistance of Drs. Whipple, Winternitz, Stevenson, and Park in the interpretation of the microscopical sections, and of Drs. Slack and Waldron for aid in the operative procedures.

DESCRIPTION OF PLATE I.

Dog XI.

FIG. 1.—Normal left adrenal removed at operation on March 31, 1913, from a female bull-dog weighing 36 lbs. Stained with Soudan III and H.

FIG. 2.—Showing hypertrophy of right adrenal which was removed at autopsy on April 14, 1913. Hypertrophy chiefly in zona fascicularis, although there is a marked increase in the size of the cells throughout the entire gland. Partial withdrawal of lipoids.

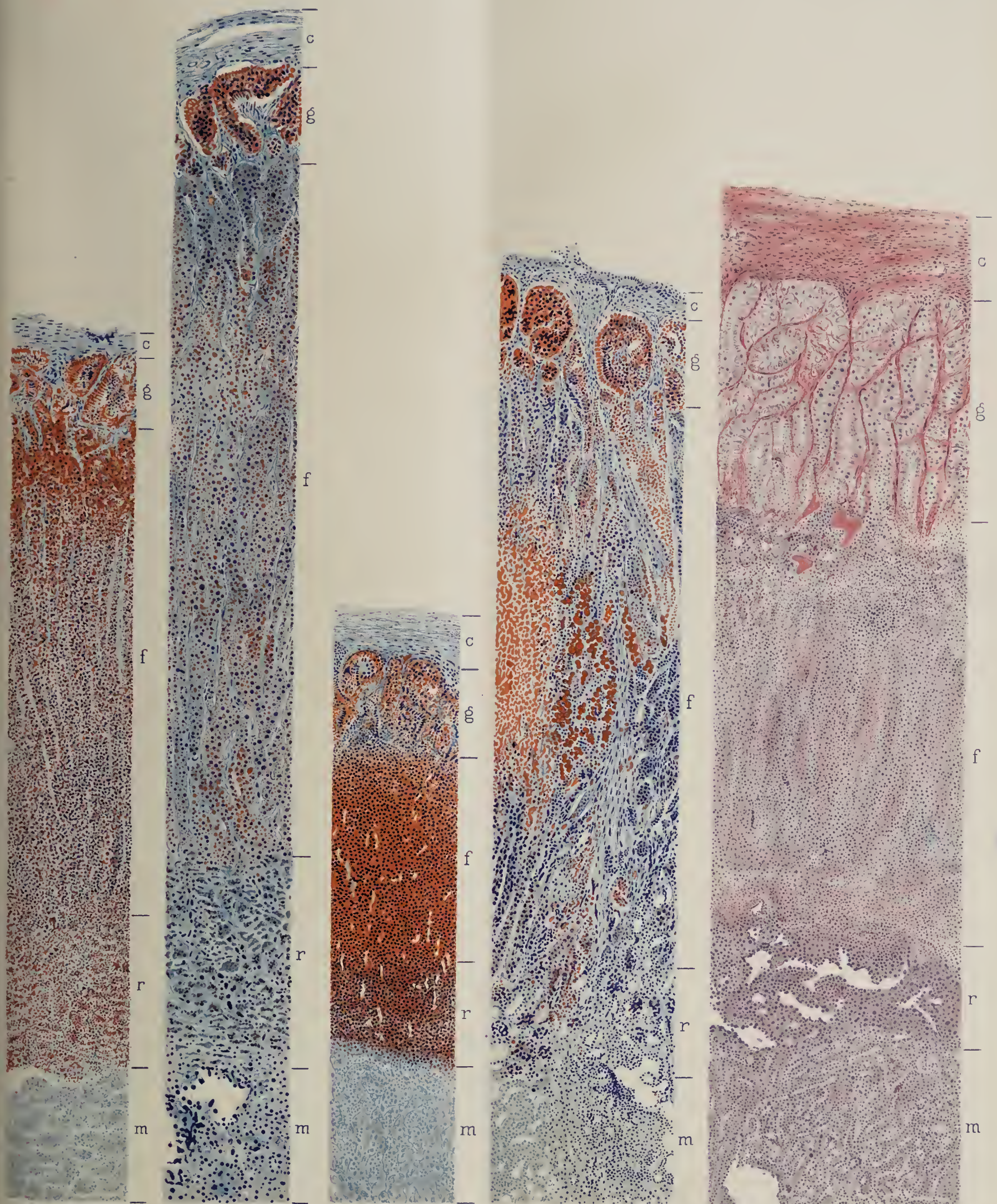
Dog VIII.

FIG. 1.—Normal right adrenal removed at operation on Feb. 19, 1913, from a male black-and-tan dog weighing 14½ lbs.

FIG. 2.—Left adrenal removed at autopsy one month later. Had chronic "distemper" which possibly accounts for the interstitial fibrosis in the zona fascicularis. Terminal pneumonia; numerous areas of focal necrosis in the zona fascicularis. No striking changes in the medulla.

Dog III.

FIG. 1.—Showing a complete disintegration of the cells of the zona fascicularis produced by ligating the larger vessels supplying an hypertrophied fragment of the right adrenal. (The entire left and 9/10 of the right had been removed at operation six months previously.) Ligation of the vessels was followed by convulsions and other symptoms of an acute adrenal insufficiency. This specimen was removed at autopsy five days after the ligation. Note the compensatory hypertrophy of the zona glomerulosa; the approximately normal looking medulla and zona reticularis.



G.W. Henry
Fig. 1.
Dog XI.

G.W. Henry
Fig. 2.
Dog XI.

H.S. Miller
Fig. 1.
Dog VIII.

G.W. Henry
Fig. 2.
Dog VIII.

G.W. Henry
Fig. 1.
Dog III.

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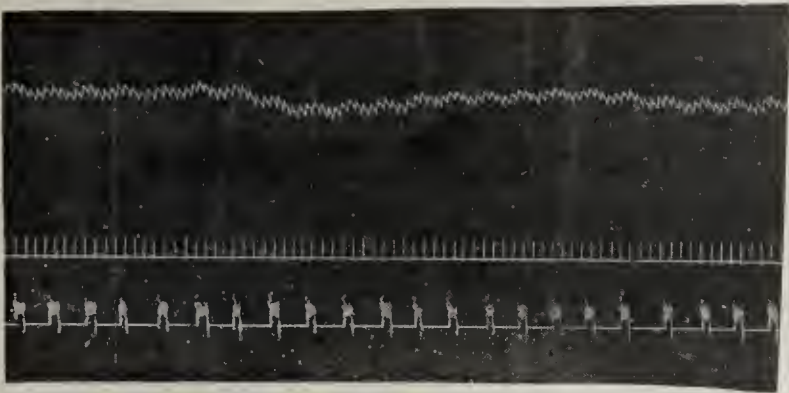


FIG. 3.—*Dog XXX*. Adrenal insufficiency. Record made 24 hrs. before death.

Pulse rate	81	per min.
Blood pressure.....	28	mm.
Respiration	18	per min.
Temperature	29°	C.

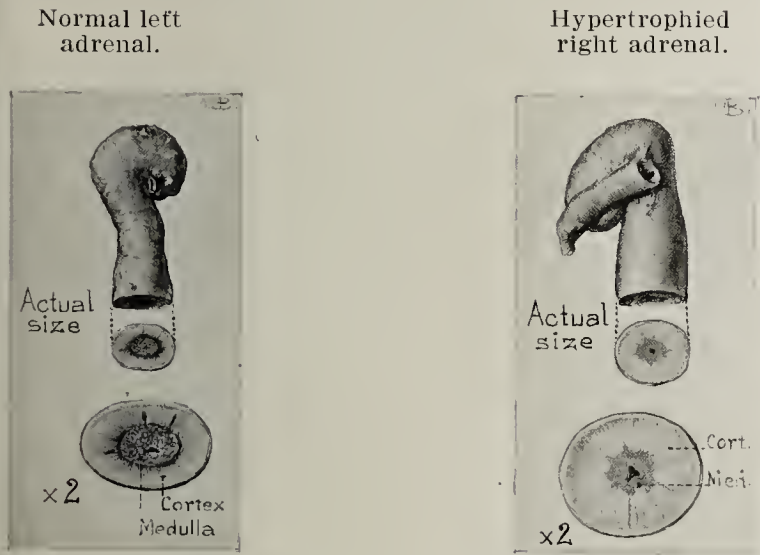


FIG. 4.—*Dog XI*. Left adrenal removed at operation March 31, 1913. Right adrenal removed at autopsy April 14, 1913. Note hypertrophy of the cortex with an apparent decrease in size of the medullary portion.



FIG. 5.—*Dog II*. The entire left adrenal had been removed and all but this small fragment at the upper pole of the right adrenal. The animal was observed for more than one year subsequent to this operation. Death followed within a few hours after the removal of this remaining fragment of adrenal.

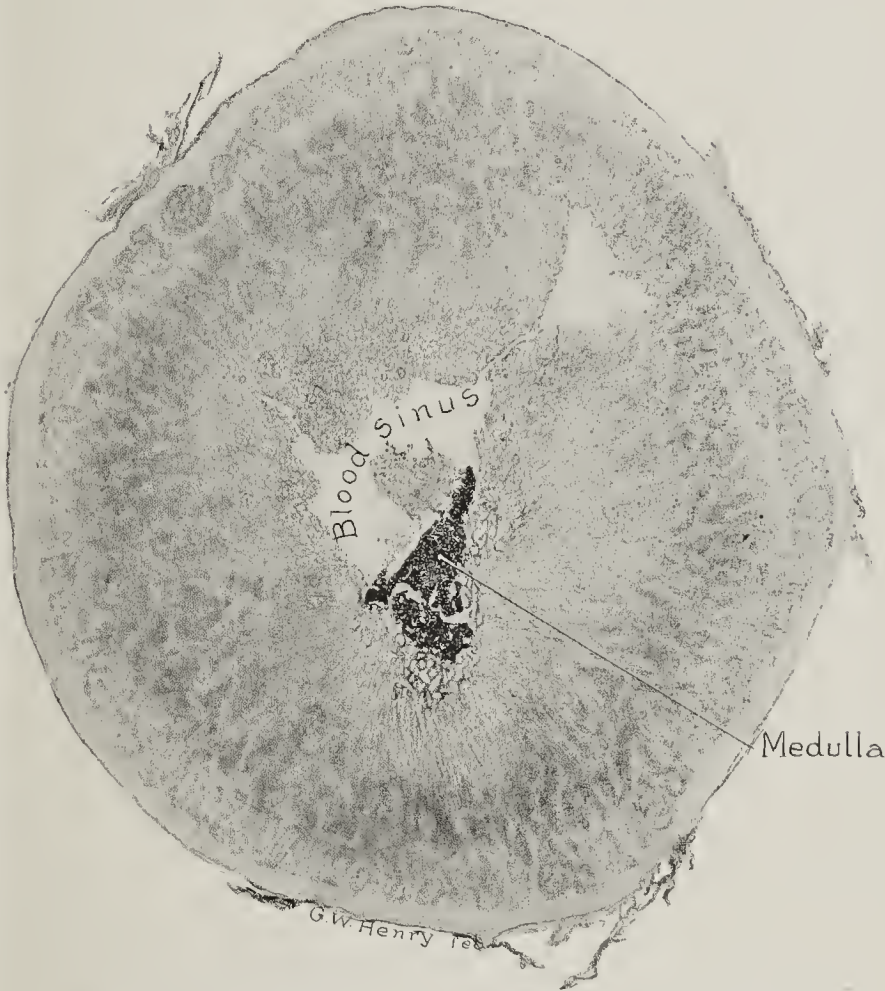
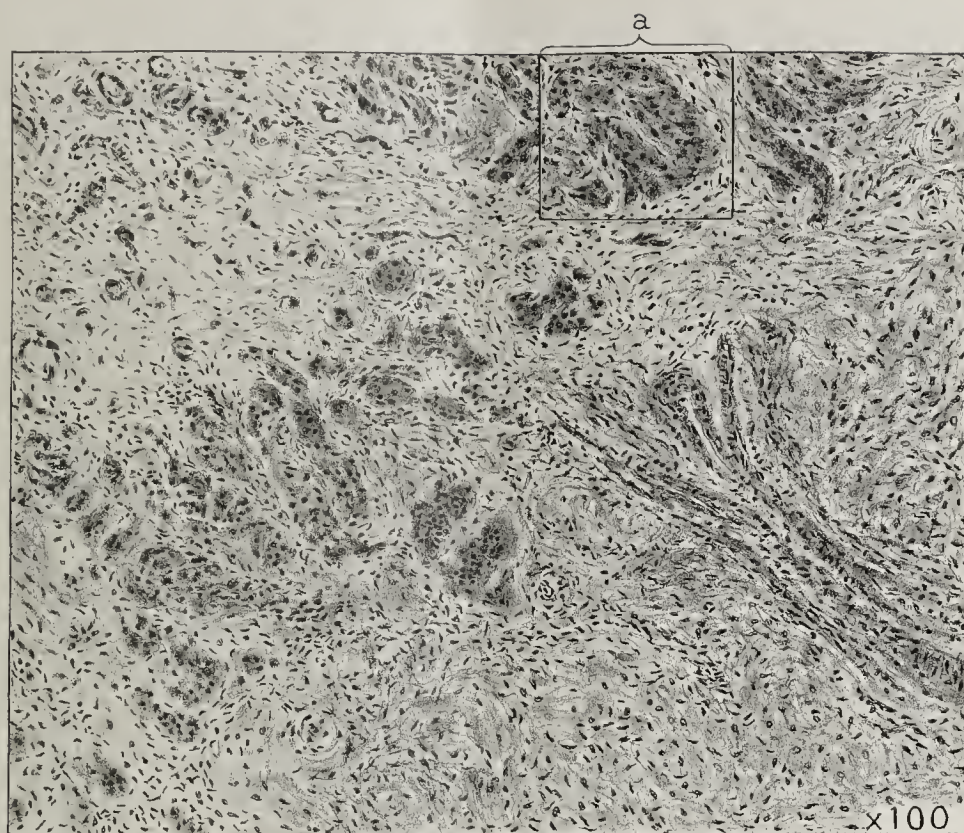


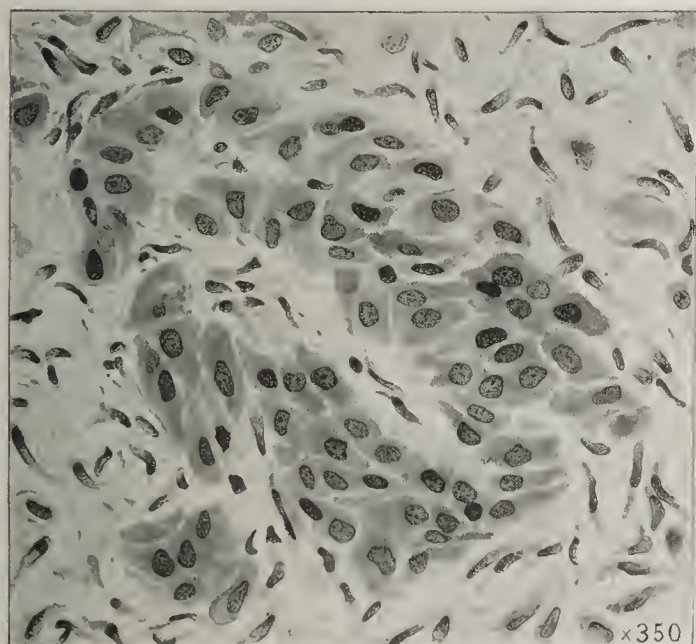
FIG. 6.—*Dog II*. Microscopic section from the fragment of adrenal shown in the preceding illustration. Note hypertrophy of cortex; absence of hypertrophy of medulla. This section represents the maximum amount of medulla in the entire fragment. During the year of observation this animal developed normally.

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G W. Henry fec.

FIG. 7.—*Dog III*. Transplant of fragment of adrenal in abdominal wall; six months duration. Medulla cells have disappeared and only those of cortex remain.



G W. Henry fec.

FIG. 8.—*Dog III*. Enlarged view of cells in preceding figure. These are lipoid-containing cells as shown by stain with Soudan III. This transplant was of no functional value since the animal succumbed a few hours after partial removal of remaining portion of adrenal.



FIG. 9.—*Dog II*. Photograph made one year after establishment of adrenal insufficiency. Has grown and developed normally.

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A CLINICAL STUDY OF PRIMARY CARCINOMA OF THE FALLOPIAN TUBE.

By CECIL W. VEST, M. D., Baltimore.

Late Resident Gynecologist, The Johns Hopkins Hospital.

Before discussing the present views as to the incidence of primary malignant disease of the Fallopian tube, it may be of interest to refer to the ideas of gynecological authorities writing only a few years ago. In 1875 Schroeder,^{64a} in his *Krankheiten der Weiblichen Geschlechtsorgane*, makes the following statement: "Carcinoma occurs in the tube never as primary and only rarely as an actual metastasis. In a case of medullary carcinoma of the right ovary, Scanzoni found the mucous membrane of the left tube infiltrated with cancer. It is evident, then, that cancerous destruction of the tubes is found only when the carcinoma from the ovary or the peritoneum, very seldom from the uterus, has involved the tubes in the degenerative process; and even then very often the tubes remain intact for a long period. Thus, in the presence of ovarian carcinoma, one not infrequently finds the tube free in the cancerous mass and it is evident that it has taken no part in the formation of the new tumor." This opinion is expressed in the various editions of this text-book which were issued during the subsequent fifteen years. In 1892 Zweifel^{177b} made the following statement: "Carcinoma of the tube is a very rare disease, except when it occurs as metastases originating from the uterus. Carcinoma of the uterus, according to its method of extension, may finally involve the tube. To describe such a tumor as primary tubal carcinoma is to represent a common occurrence as if it were an interesting and rare one." One of the most comprehensive articles of the later works on this subject is to be found in Martin's⁸⁹ *Krankheiten des Eileiter*.

The first case of primary tubal carcinoma was published by Orthmann^{72a} in 1888 and was followed by Doran's^{22a} case in the same year and by Kaltenbach's^{48a} in 1889.

With the development of surgery and the accompanying advancement in the study of the clinical and pathological material many other cases have been reported. Peham,⁷⁵ in 1903, collected 63 cases; Orthmann,^{72b} in 1906, 84; Doran,^{22a} in 1910, 100; and in 1911, Anduze-Acher³ published his thesis, in which he had tabulated no less than 115 cases. Since then the number of reports has increased until, with those included in the present paper, 132 cases of primary carcinoma of the tube are to be found in the literature. Hence it is evident this condition is not so unusual as was formerly thought, and the gynecologist, when dealing with an adnexal tumor, must always take into consideration this possibility.

The two principal theories which have been advanced for the explanation of this neoplasm are those by Doran and Fearn and by Sanger and Barth.* These authorities are of opinion that a previous inflammation of the part is the provocative factor.

Doran and Fearn believe the carcinoma represents a malignant change which has taken place in a benign papillomatous

condition consequent to an earlier salpingitis. Roberts's^{82a} first case is a good example of this view. Upon macroscopic examination, the tube was seen to be filled with a papillary growth which at first was thought to be benign, but which microscopic examination showed to be malignant. The patient had had gushes of sanious fluid and a similar fluid was found in the tube.

Sanger and Barth's* theory is that the carcinoma arises upon the basis of a chronic, probably purulent, inflammation. This change does not occur in the presence of a recent condition, but after a long lapse of time, for the most part about the climacterium.

In view of the fact that an inflammatory condition was held to be an etiological factor in the causation of tubal carcinoma, an attempt was made to ascertain from the published cases whether or not any inflammatory changes in the pelvic structures were found at operation. Unfortunately in many cases the descriptions were meagre and in others no mention at all of this condition was to be found in the reports of the macroscopic or microscopic examinations, making it impossible to obtain any valuable data on this point. Again, when a small amount of inflammatory change was present at operation, it was often quite impossible to decide whether this had existed previous to the appearance of the new growth or was a result of its extension.

As to pregnancy, a record was found in 112 cases. Of these women 79 had become pregnant; 73 had been delivered of living children. Six patients had aborted and had had no other pregnancy. In all, 17 patients had aborted. Thirty-three were nulliparæ. Of the women who were delivered, 32 had had one child. Of the multiparæ, one patient had had seven children and another ten.

In an attempt to ascertain whether or not the patients had suffered from any tubal inflammation, the following deductions were made from the clinical data: In only a small number of the cases reported was there any history of a pelvic inflammatory disease. Since 70 per cent of the women became pregnant, it may be considered they were free from salpingitis; or if they were infected, the condition was either unilateral or not sufficient to prevent conception, or it had developed after delivery. Assuming that the 32 primiparæ (*i. e.*, 28.4 per cent of all the cases) suffered from a subsequent infection (the so-called one-child sterility) and that the 33 women without children were sterile from tubal inflammation, we should have a total of 57.7 per cent of the women who, at some time, had had a tubal infection. This leaves 42.3 per cent of the cases of primary carcinoma of the tube in which no previous inflammatory condition existed in the tube, and these

* Cf. Martin: Ref. No. 89.

cases must be explained in some other way. It is difficult to draw conclusions and this comparison of course is only theoretical and does not pretend to any accuracy, especially as so many conditions may enter into and modify the results. For instance, in the nulliparæ, the question of sterility of the male must be considered, while in the parous women the prevention of further conceptions must be considered. Again, whether the patient is married or single must be taken into account.

Thus:

Of 112 women,	
79 or	70.3% became pregnant.
Of the 79, 32 or	28.4% had one child.
33 or	29.3% did not become pregnant.

Considered sterile from inflammation.. 57.7%

Considered not to have had previous inflammation 42.3%.

In over 19,000 patients who have been treated in the gynecological wards of The Johns Hopkins Hospital, and in whose cases specimens from every piece of tissue removed have been examined microscopically, a large number showed inflammatory changes in the tubes. Many of these women had had the inflammation for many years, yet among this number there have been only four cases of primary tubal carcinoma. If a previous tubal inflammation is a primary factor in the causation of this condition, we should certainly expect a much larger proportion than four in a total of 19,000 cases. Hence we must conclude that inflammation of the tubes plays a minor rôle, if any, in the development of carcinoma of the uterine tubes.

Age.—Whether there was a pre-existing condition of inflammation in the tubes or not, it is obvious that the time of occurrence in these cases corresponds with that of malignancy in other parts of the body or with what may be termed the "cancer age." The ages are given in 127 cases. In sixty-eight, or 53 per cent of the patients, the condition occurred between the ages of 40 and 50, and it was observed thirty-eight times in the latter half of this period, the average age being 48.3 years. The youngest patient (27 years old) in this series is the one mentioned by Norris.⁷¹ Pawlik's⁷² patient, the oldest, was 70 years old, and had also borne the greatest number of children, having been delivered ten times.

The incidence at the various ages arranged in quinquennial periods is as follows:

27 to 30— 3 cases	
30 to 35— 3 cases	
35 to 40—11 cases	
40 to 45—30 cases	} 53 per cent of all the cases
45 to 50—38 cases	
50 to 55—19 cases	
55 to 60—18 cases	
60 to 65— 4 cases	
65 to 70— 1 case	

The types of carcinoma observed have been variously described and classified. Of these classifications Sanger and Barth's * was the first one published and is the one referred to

by most authors. Two forms are differentiated:

(a) Papillary.

(b) Papillary-alveolar, which corresponds to adenocarcinoma of the uterus.

Friedenheim's classification is as follows:

1. Mucous-membrane carcinoma:

(a) Papillary.

(b) Papillary-alveolar.

2. Wall carcinoma.

(a) Alveolar.

Falk's arrangement is:

(a) Benign papilloma.

(b) Malignant papilloma.

(c) Papillary epithelioma.

But although various classifications have been offered, as in dealing with cancer of the fundus uteri, it is better that one variety of carcinoma of the tube be considered. Although in the same specimen at one place a papillary and at another an alveolar arrangement will be seen, the papillary form is characteristic of this condition.

The middle and outer thirds of the tube are most often the site of the carcinoma and are altered in size. The uterine end is seldom changed, except as a result of the dilatation of the tube and proliferation of the neoplasm. The tube is filled with the cancerous mass and becomes distended, being retort or sausage-shaped and often assuming quite large proportions.

Changes in the tube wall are of interest, especially when compared with carcinoma of other hollow organs, in which extension through the outer wall is not unusual.

In malignancy of the tube definite changes may take place in the muscular layer. This portion may be thickened, as is seen in Case 2, or, as the result of the distention of the tube and pressure of the new growth, this layer may be much thinned, the wall being scarcely 2 mm. in thickness and macroscopically composed of a few muscle fibers and the peritoneal covering. Such a condition is seen in Case 3. In each instance there may be an invasion of the wall of the tube by the growth, but actual perforation of it by the neoplasm in its enlargement is rare. In Schäfer's⁷³ case and Spencer's⁷⁴ Case 2, the growth had extended through the peritoneal covering.

In the cases reported by Cullen⁷⁵ and Karakoz⁷⁶ each tubal mass measured 14 cm. in diameter, while in Gurd's⁷⁷ case it was 12 cm. The specimen removed in Stolz's⁷⁸ case is described as being as large as a foetal head. The last-mentioned specimen presented quite an unusual picture, the uterine end being closed with carcinoma. The outer portion of the tube was buried in the cul-de-sac and was adherent. The fimbriated end was open.

As the distal end of the tube provides a way for the immediate escape of carcinoma cells, it is important to note the condition of the abdominal ostium when an early case is seen at operation. With the increase in amount of the tumor, the tube becomes filled with the carcinoma, which may partially or completely close the abdominal ostium. The ostium may also be closed as a result of inflammatory reaction. With

* Cf. Martin. Ref. No. 89.

carcinoma in the outer end of a tube whose ampulla is open, particles of the tumor can very readily be carried directly into the peritoneal cavity. When the end is closed immediate outward extension is prevented, unless there has been an escape of the cells before the end has become occluded. From our two cases seen at operation, there was proportionately more involvement of the peritoneum than of the lymphatic glands. This result was to be expected inasmuch as the carcinoma cells would naturally follow the line of least resistance. The peritoneal metastases occur for the most part by direct implantations.

In this way, traversing the path followed in transmigration of the ovum, these metastatic cells become lodged in the opposite tube. Herein doubtless lies the explanation of the large number of cases in which the growth is found to be bilateral. From the descriptions of the tubes in these cases, it would seem that the tumors were about the same size on each side and there is nothing to indicate which tube was primarily involved. Hence one is led to believe that the cells are dislodged and reimplanted early in the development of the primary growth.

The case reported by v. Rosthorn⁸⁷ is a good example of implantation in the opposite tube. A carcinomatous right tube was removed, but recurrences were noted in six months. A second operation became necessary and pelvic metastases were found. A small cancerous nodule was present in the left tube.

Glendening⁸⁸ found carcinoma cells in the lumen, in the subepithelial tissues of the lining folds and in the various layers of the tube. The sections were taken from the different parts of the tubes at operation from patients suffering from carcinoma of the stomach.

A longitudinal section of a carcinomatous tube shows it to be filled with a grayish-white granular mass. The tumor may form a homogeneous mass or in parts be raised in papillary or cauliflower-like growths. The central portion is often filled with a serohemorrhagic or purulent fluid. Areas of necrosis may be seen throughout the tumor in advanced cases.

As is to be expected, the new growth is found as often in the right tube as in the left, and it is interesting to note the large number of cases in which both tubes are implicated. About 26 per cent of the cases showed a bilateral malignant involvement, and in many of these cases there was no marked disproportion in the size of the tumors.

Thus, as regards the site, the right side was involved in 44; the left in 45; both sides in 36 cases. In two cases the growth is described as being unilateral; in four instances no mention is made of the side implicated.

Recurrence.—Carcinoma of the tube, while of fairly slow growth before the symptoms are pronounced, is highly malignant. The recurrences became evident soon after the operation, even in some cases in which it was thought that all traces of the disease had been removed. This is, of course, due to the extensiveness of the growth, metastases having been present in the peritoneal cavity and lymphatic system at the time of operation. The recurrences were primarily abdominal and took the form of large masses surrounding the vessels and nerves

of the pelvis; there was also an enlargement of the peritoneal implantations and retroperitoneal glands with a consequent ascites. In showing how far removed metastases may be found, Rossinsky's⁸⁹ case is interesting. At the time of operation, a nodule was noticed in the left supraclavicular region, which after three months had become the size of an apple. It was excised and showed carcinoma. In v. Rosthorn's⁸⁷ case, a recurrence occurred in the vaginal incision, while in the second case reported by Spencer⁹⁰ the abdominal incision showed a new growth. Recurrent carcinoma has also been noticed in the uterus, bladder, vagina, liver, diaphragm, and omentum.

In the following table the patients had had a recurrence or had died from the disease:

DEATH OR RECURRENCE.

Within three months after operation.....	10
From the third to sixth month.....	11
From the sixth to twelfth month.....	24
During the second year	8
After the second year	5

Of the 132 patients, only four were well after five years and may be counted as cured: Wiesinger's¹¹² case after thirteen years, Zangemeister's¹¹⁵ after eight, Benthin's⁷ and Veit's¹⁰⁵ after seven. Five patients were well after three years and four after twenty-six months.

Symptoms.—The advanced condition found when the patient is referred for operation is probably to be explained by variation and irregularity in the occurrence of symptoms or failure to recognize those present early in the disease. Unfortunately the definite symptoms found in carcinoma of the uterus are often lacking where the tube is primarily implicated. There are, however, certain points associated with this condition which should be remembered and malignancy of the uterus or adnexa should be suspected when certain symptoms are present. Most commonly associated with this condition are a watery, vaginal discharge, often sanious, abdominal pain and menstrual disturbances.

At the onset of the disease the discharge, which is usually the first symptom noted, may be leucorrheal and blood-tinged in character, appearing as a continuous copious flow or in periodic gushes. It may be acrid and malodorous. Eglington's²⁶ case is of special interest, inasmuch as the discharge had been noticed for thirteen years. The carcinoma, of course, was not present during this time, but probably made its appearance in the year previous to operation, during which time the discharge was worse. The pain is often referred to the hypogastric region or is general throughout the abdomen and frequently is colicky in character. At other times it may be especially localized in one of the lower abdominal quadrants, but radiates to the upper abdomen, back and legs, later becoming constant and severe. Associated with these symptoms distention of the abdomen or a hypogastric tumor may be made out. The tumor may extend nearly to the umbilicus and be the first thing of which the patient complains. It is not unusual to have menstrual disturbances, such as menorrhagia,

metrorrhagia or a reappearance of vaginal bleeding after the menopause.

A profuse, blood-tinged discharge, abdominal pain with or without an abdominal tumor and menstrual disturbances are the characteristic features of this condition.

Loss of weight, cachexia, ascites, painful urination and defecation frequently appear late in the disease. When a patient gives such a history, though no abdominal tumor is to be made out, the presence of some malignant growth in the generative tract must be considered. The uterine curettings will doubtless be negative, but a careful pelvic examination should be made, if necessary under anæsthesia, when unilateral or bilateral thickening, if not an enlargement or tumor, is quite likely to be made out. When a patient describes such symptoms as have been enumerated and a pelvic tumor is found, it is better to attempt its complete removal through an abdominal incision rather than empty its contents through a pelvic puncture. A lateral tumor suspected of being a tubal carcinoma should not be emptied or examined by a vaginal incision. The tubal mass may be in the upper part of the pelvis or behind the uterus, filling the cul-de-sac. On palpation, it will be firm, rounded, transmitting a doughy or fluctuating sensation. Many tumors have been quite hard and tense, so that a diagnosis of myoma uteri was justifiable. In some instances the tumor was adherent. In a woman of middle age, the presence of a lateral tumor with ascites, even of short duration, should arouse a strong suspicion of malignancy. Ascites does not, as a rule, occur as early as in ovarian tumors and probably is more common in association with the latter growth. Pelvic metastatic nodules may be made out on vaginal or rectal examination. It is quite difficult, often impossible, to differentiate this condition from a malignant ovarian tumor, especially if metastatic nodules are present on the pelvic peritoneum. Such a tumor should, however, be considered malignant. In making a pelvic puncture, if blood-stained, watery fluid is obtained from a lateral tumor, the abdomen should be opened, a positive diagnosis made and a complete operation done if necessary. Care should be taken at operation lest what is thought to be a hydro- or hæmatosalpinx prove to be a tube containing a malignant growth, because if this is ruptured and its contents scattered throughout the lower part of the abdominal cavity the prognosis becomes infinitely worse.

That the possibility of the co-existence of tubal malignancy with an ovarian cyst must not be disregarded is shown by the first case of our series. Only after the operation for the removal of the cyst was the malignant tumor found. In Knauer's^{53a} and Savor's⁵⁰ cases the cysts were known to have been present for eighteen years, whereas the immediate symptoms had only appeared within one year. Ovarian cysts were also present in the cases reported by Dirner,²¹ Orthmann,^{72d} Mériel,⁶⁴ Doran,^{22d} Cullingworth,¹⁶ Warneck¹⁰⁸ and Wiesinger¹¹² (third case). In Warneck's case the cyst was twisted twice on its pedicle.

The phases of rapidity of growth and metastasis are important and especially interesting from the clinical standpoint.

Nineteen patients were operated upon within four months from onset of symptoms.

Thirty were operated upon between the fifth and eleventh months.

Thirty-four were operated upon between the twelfth and the twenty-fourth months.

Eight in the third year.

Two in the fourth year.

As mentioned above, in one case certain symptoms were present thirteen years, and practically half of the patients allowed at least a year to elapse before an operation was performed. Thus it is seen that some of the tumors are not especially rapid in their growth. The delay in seeking medical advice is probably due to the fact that the patient thought the symptoms were natural or unimportant, and, the part involved naturally not permitting of inspection, the condition was disregarded, until the neoplasm had extended beyond the possibility of removal.

The meaning of these symptoms must be thoroughly recognized by the practitioner and a patient having such complaints must be submitted to a careful pelvic examination in order that the possibility of a uterine or tubal carcinoma may be excluded. It is of equal importance that the laity should know of these symptoms and their meaning, so that women having a profuse vaginal discharge, leucorrhœa or blood-tinged, will understand the necessity of an early vaginal examination. In this way many cases of malignant disease of the uterus or tubes will be detected while there is still a great probability of a cure. When a woman complains of the symptoms here described and the uterine curettings show no malignant change, though nothing be made out on pelvic examination, carcinoma of the tube or a pre-cancerous lesion should be suspected.

The change in the tube known as hydrops tubæ profluens, or by the old writers as "dropsy of the tube," although not often seen, should be mentioned here. In this condition, the fimbriated extremity is closed and the lining membrane secretes a colorless, watery fluid. The hydrosalpinx may attain to quite large proportions, and become the size of a child's head or larger and palpable through the abdominal wall, before the contained fluid comes away. After the tubal contents have been expelled through the uterus and vagina, the tumor is much reduced in size. After refilling, the tube will again spontaneously empty itself. A discussion of the condition of hydrops tubæ profluens with the enumeration of several cases is contained in Edelberg's²⁵ article. In carcinoma of the tube the discharge is also frequently intermittent, which accounts for the association of these two conditions. In fact, some authors believe this form of hydrosalpinx to be a preliminary condition in the malignant tubal growth.

Prognosis.—So far as the rapidity of the growth, metastases and recurrence are concerned, carcinoma of the tube is quite comparable to carcinoma of the fundus uteri. The prognosis, however, owing to the advanced stage at operation, has been anything but encouraging. Only four patients are known to be well after five years. But should these cases be seen by the gynecologist in the early months of the symptoms, the hope

of a permanent cure should not be much less than in cases of uterine cancer or malignant growth of other operable viscera.

Treatment.—In carcinoma of the tube, a panhysterectomy and a double salpingo-oöphorectomy are indicated, together with a wide removal of the broad ligament on the side involved. In some instances, the existence of the carcinoma in the adnexa was not recognized until the material was studied microscopically. In several of these cases the abdomen was reopened and the complete operation performed.

Where the pelvic glands are enlarged and can be dissected out without unduly prolonging the operation, it may be of material advantage to remove them, if the retroperitoneal glands are not enlarged. But whenever there is a glandular involvement, as in uterine cancer, the growth has then doubtless extended beyond the hope of permanent cure by surgical aid. That the enlargement of the glands is due to inflammatory origin is much less probable than in uterine cancer.

In inoperable cases, when the carcinoma is causing pain from involvement of pelvic structures, as much of the mass as possible should be removed for the sake of temporary relief. This was done in one of our cases. The bisection operation was found to be the most advantageous method of removal.

As shown by Poirier,⁷⁵ the lymphatics for the tube and upper portion of the broad ligament are the same as those for the fundus, this area being supplied with two sets of vessels, which course between the folds of the broad ligament. The lymphatics leave the cornu of the uterus and as they go lateralward are situated to the inner side of the tube. In the infundibulopelvic ligament, they follow the course of the ovarian vessels and drain into the lumbar glands of the same side. This set of vessels and glands are most often involved in the extension of the tubal cancer through the lymphatics. The other lymphatics are directed anteriorly, following the round ligament and drain into the external iliac and the inguinal glands.

The lymphatics from the cervix and base of the broad ligament go to the lateral wall of the pelvis, to the external iliac and hypogastric glands and posteriorly to the lateral sacral and promontory glands.

In only a small number of cases did the inguinal glands show metastatic growths, the pelvic and retroperitoneal glands being the ones most generally involved.

Metastases to the diaphragm are not uncommon, but in only two instances are liver nodules mentioned. These are to be found in Fonyó's³³ first case and Wiesinger's¹²² second case. These two patients died on the second and third day, respectively, after operation, and the secondary growths were found at autopsy. Four nodules were found on the upper surface at operation in our Case No. 2. This is the only case noted in which liver metastases were observed at operation.

A table of the reported cases of tubal carcinoma was practically completed when Doran's²²⁴ second paper was obtained. The table in this article completes one hundred cases which the author had collected from the literature. These articles (by Doran) are readily obtained and to avoid repetition the cases included in them have been omitted from the table here published. Only the cases which are not included by him and

those that have appeared since are given. The cases of Speneer, Tate, Legg and Boxer are mentioned by Doran.

The fourth case which has been observed in The Johns Hopkins Hospital was reported by Schenck. An outline of this case is given in the table as Case No. III.

Demonstration of specimens of tubal carcinoma are reported by Amann,¹ Baisch^{6a} and Penkert.⁷⁸

Since the article was finished a detailed account of Baisch's case reported by v. Raabe,^{6b} has been obtained and two cases have been reported. Baisch's case is as follows: Age 47; one child; menses regular until past three years, when flow became irregular; was increased in amount and lasted eight days. Flow has been increasing past two years.

Operation.—Hysterectomy, double salpingo-oöphorectomy. There was an intraligamentary ovarian cyst on the left side. The contents were evacuated, and during the removal of the pelvic structures the carcinomatous tube (left) was ruptured. No metastases were found at operation.

Macroscopic Examination.—Left tube, sausage shaped; contains carcinoma. Right tube, tortuous, hydrosalpinx.

Microscopic Examination.—Primary carcinoma. Papillary alveolar form with tubo-ovarian cyst. Metastases in uterus and ovary. Eleven months later, second operation for recurrence in abdominal wall, to left of median line. None in peritoneal cavity. Tumor, papillary alveolar in character. The clinical findings in this case are quite comparable to the condition found in Case I of our series.

Drutmann.²³ Patient, age 54; menopause four years. Had a blood-tinged, serous discharge for two years. A curetment was first done and from the material examined microscopically a diagnosis of carcinoma fundus uteri was made.

Operation (Döderlein).—Hysterectomy, double salpingo-oöphorectomy. Uterus contains three small subserous myomata. Ovaries atrophic. Tubes are normal except for a tumor the size of a pea in the portion of the right tube in the myometrium. On section, tumor was yellow in color and of butter-like consistency.

Microscopic Examination.—Tumor was a carcinoma of adenomatous type.

This case was operated on probably the earliest of any of the series here discussed.

Lipschitz.⁵⁹ Nullipara, age 44. Menses were irregular. Well until one year before operation, during which time patient had severe pain in back at menses. For about a year patient had abdominal pain on walking.

Operation.—Hysterectomy, double salpingo-oöphorectomy.

Macroscopic Examination.—Left tube normal. Outer part of right tube is dilated and contains a tumor the size of a hazel nut. Ampulla is closed. Uterus contains a small interstitial myoma.

Microscopic Examination.—The right tube contains tubercular inflammatory tissue, numerous papillary forms and carcinoma of the alveolar type. In the arrangement of the microscopic picture it is thought the carcinoma developed on the base of the old tuberculosis.

TABLE OF CASES.

Author.	Age.	Para.	Menses.	Symptoms.	Tube.	Operator and Operation.	Fimbriated end.	Metastases at operation.	Description.		Recurrence.
									Macroscopic.	Microscopic	
1. Roche.	44	2	Regular.	Metrorrhagia assoc. with abdominal pain.	Left.	(Boursier) Hysteromyomectomy. (Bisection) Double salpingo-oöphorectomy.	Large tubal tumors, cystic and brownish-red in color. Wall thin and tense. Left, size of small orange.	Carcinoma.
2. Dandelski.	64	1 1 abortion.	Regular. Menopause at 48.	Pain in right side of abdomen and sacro-iliac region.	Right and left.	Hysterectomy. Double salpingo-oöphorectomy.	Left, closed. Right, adherent in pelvis.	Left, tumor is in outer third of tube and is size of dove's egg. Right, white cauliflower-like mass.	Adeno-carcinoma.	Well, 3 months later.
3. Sehenek.	53	4	Menopause at 50.	Pain in lower abdomen 2 yrs., assoc. with thin, blood-stain'd, offensive discharge.	Left.	Left salpingo-oöphorectomy.	None.	Tube filled with new growth. Distal end dilated.	Adeno-carcinoma.	Well, 3 months later.
4. Kundrat.	47	1 abortion.	Regular. Menorrhagia past 2 yrs.	Abdominal tumor 4 yrs. Rapid increase past 2 mos.	Right.	(Wertheim) Hysterectomy. Double salpingo-oöphorectomy.	Filled with carcinoma.	Middle and outer parts filled with new growth. Abdominal end communicates with ovarian cyst.	Papillary carcinoma.
5. Benthin.	40	1	Regular.	Menstrual flow foul-smelling past year. Abdominal pain six months.	Right.	(Pfannenstiel?) I. Right salpingo-oöphorectomy. II. Hysterectomy. Left salpingo-oöphorectomy.	Closed.	None.	Tube is retort-shaped and filled with a brownish, cauliflower-like mass.	Papillary alveolar carcinoma.	Well, 7 years.
6. Rossinsky.	44	3 2 abortions.	Regular.	Abdominal pain.	Left.	(v. Herff) Left salpingo-oöphorectomy.	Atresic, adherent to ovary.	Left supra-clavicular gland palpable.	Tube pear-shaped, cystic. Filled with papillary growth.	Carcinoma cylindro-cellulare.	Supraclavicular node in 3 months size of an apple. Excise show carcinoma.
7. Cullen.	46	1 miscarriage.	Regular until last 3 mos. since when profuse. Past yr. profuse, leucorrheal discharge assoc. with blood and some odor.	Cramp-like pain in R. I. F. 2 yrs., left side 1 yr. Radiates to legs.	Right and left.	(Kelly) Hysterectomy. (Bisection) Double salpingo-oöphorectomy.	Right filled with new growth.	Right tube distended and sausage-shaped, 14 x 12 x 10 cm. Left dilated to 4 cm., contains new growth in middle portion.	Adeno-carcinoma.	After 3 yrs.
8. Spencer.	64	Multi-para.	Regular. Menopause at 48.	Greenish offensive discharge.	Left.	Hysterectomy. Double salpingo-oöphorectomy.	Closed.	Growth in upper portion of vagina.	Outer part of tube distended and contains a warty-like growth, the size of a pigeon's egg.	Carcinoma.	Died the day after operation.
9. Spencer.	35	0	Irregular and profuse.	Abdominal tumor 18 mos., pain 4 mos.	Left.	Left salpingo-oöphorectomy.	Closed.	Intestinal.	Distended and filled with a whitish, brittle growth.	Carcinoma.	Abdominal and in incision. Died after 1 yr.
10. Spencer.	58	1 3 abortions.	Regular. Menopause at 48.	Enlargement of abdomen, pain.	Left.	I. Left salpingo-oöphorectomy (marked ascites). II. 3 mos. later (Exploratory laparotomy).	Open.	None.	Tube forms outer wall of yellowish-white carcinomatous mass.	Papillary carcinoma.	3 months.

TABLE OF CASES.—Continued.

Author.	Age.	Para.	Menses.	Symptoms.	Tube.	Operator and Operation.	Fimbriated end.	Metastases at operation.	Description.		Recurrence.
									Macroscopic.	Microscopic.	
Walter-Tate.	52	3	Menopause at 48.	Yellowish, blood-tinged discharge. 2 yrs. assoc. with pelvic pain.	Right.	Bilateral salpingectomy.	None.	Somewhat tortuous and cavity filled with soft friable growth.	Adeno-carcinoma.	Well, 27 mos. later.
Walter-Tate.	44	0	Regular until past 18 mos., since when flow has been scant.	Metrorrhagia for 3 mos. assoc. with pain in back and hips. Loss of weight.	Right and left.	Double salpingo-oöphorectomy. Appendectomy.	Omental.	Right tube tortuous, wall contains plaques of growth. Left distended and contains new growth.	Columnar-celled carcinoma of both tubes. Metastases to omentum and right ovary.	Left hospital on 23rd day.
Legg.	42	—	Regular.	Abdominal pain and blood-stained discharge 2 years.	Right and left.	Double salpingo-oöphorectomy.	Left, closed. Right not made out.	Pelvic?	Left, tubo-ovarian cyst. Both tubes dilated and filled with yellowish-white carcinomatous mass.	Papillary carcinoma.	Well, 26 mos. after operation.
Boxer.	62	1	Regular. Menopause at 51.	Blood-stained, watery discharge for 6 mos. Was fetid and purulent. Cramp-like pains 3 weeks.	Right and left.	Hysterectomy. Double salpingo-oöphorectomy.	Left, closed. Right, communicates with tubo-ovarian cyst.	Omental and peritoneal.	Left, thickened and filled with brown tumor mass. Right, retort-shaped. Outer part filled with friable tumor mass.	Papillary alveolar carcinoma.	Well, 1 mo. Died after 6 mos.
Vignard.	42	1	Regular. Amenorrhea 6 mos.	Violent, radiating abdominal pain 3 yrs.	Left.	Double salpingo-oöphorectomy. 4 liters ascites.	Infiltration of rectal peritoneum.	Left tube enlarged and filled with new growth. Right normal size. Some vegetations on outer surface.
Montgomery.	34	0	Regular.	Whitish discharge. Premenstrual pain. Profuse menses.	Right.	I. Right salpingectomy. II. Hysterectomy left salpingectomy.	None.	Right, thickened in middle portion. Left, thickened.	Cylinder-celled carcinoma.	Well, 8 mos. after operation.
Weinbrenner	43	1 miscarriage.	For 1 year cramp-like abdominal pain followed by bloody, watery discharge.	?	Hysterectomy, salpingectomy.	Tube filled with carcinoma.
Feehey.	30	1	Irregular.	Repeated hæmorrhages.	Right.	I. Right salpingectomy. II. Partial left salpingectomy; right oöphorectomy 3 wks. later	Fungating mass in tube.	Carcinoma.
Eglinton.	47	2	Menopause at 44.	Blood-tinged watery discharge 13 yrs. Worse past year. Increased on voiding.	Left.	Left salpingo-oöphorectomy.	Filled with friable carcinoma.	Tube distended, retort-shaped.	Carcinoma. Some individual cells like sarcoma.	After 7 mos.
Murd.	46	5	Regular.	Profuse, watery, slightly purulent discharge.	Left.	Left salpingo-oöphorectomy.	Tumor 12 x 8 x 7 cm. in middle of tube.	Carcinoma.	Well, 7 mos. after operation.

TABLE OF CASES.—Continued.

Author.	Age.	Para.	Menses.	Symptoms.	Tube.	Operator and Operation.	Fimbriated end.	Metastases at operation.	Description.		Recurrence.
									Macroscopic.	Microscopic.	
21. Fonyó.	50	2 1 abortion.	Regular, profuse flow. Menopause at 48.	Thin, watery, blood-tinged discharge for 2 yrs. Abdominal tumor.	Right and left.	Double salpingo-oöphorectomy.	Onenodule on upper surface of liver (autopsy).	Tubes enlarged and filled with solid white tumor. In part cystic degeneration.	Papillary carcinoma.	Died 2 day. Peritonitis.
22. Fonyó.	56	3	Menopause at 51.	Abdominal tumor with pain 3 yrs. Thin, odorless discharge one yr.	Right.	Right salpingo-oöphorectomy.	None.	Tube enlarged and filled with tumor, which for the most part is dark yellow in color.	Papillary alveolar carcinoma.	Well, after yrs.
23. Karakoz.	55	2	Regular. Menopause at 50.	Profuse vaginal discharge. Retention of urine.	Left.	(Schirschow) Left salpingo-oöphorectomy.	Free.	Tube sausage-shaped, distended. 14 cm. dia. in middle portion, cystic.	Papillary carcinoma.
24. Bertino.	48	1	Regular. Menopause at 46.	Profuse white discharge. Small in amount at first. Abdominal enlargement. General weakness.	Right.	(Resinelli) Right salpingo-oöphorectomy.	Tube very much dilated. New growth attached to base of tube. Ovary free.	Papillary carcinoma.
25. Wiesinger.	56	1	Menopause at 51.	Abdominal tumor and pain 3 years. Bloody, watery, odorless discharge. Severe pain.	Right.	(Dirner) Right salpingo-oöphorectomy.	Tube 5 cm. in dia. in middle portion. Nodules on outer surface. Tube filled with yellowish tumor, a few points showing coagulation necrosis.	Papillary carcinoma.	Well, 13 yrs.
26. Wiesinger.	50	2 1 abortion.	Profuse and painful for 2 years.	Watery flow after periods. Has noticed a tumor 2 yrs.	Right.	Right salpingo-oöphorectomy.	Open.	Omental and intestinal. Diaphragm and liver (autopsy).	Tube thickened and distended. Some areas of degeneration. Tube filled with carcinomatous mass. Small spaces filled with blood.	Papillary carcinoma.	Died 3d day. Sepsis.
27. Wiesinger.	40	0	Amenorrhea 2 mos.; previously profuse flow 5 mos. Stopped by curettement.	Sick 10 mos. Metrorrhagia 3 weeks before operation. Pain in back.	Right and left.	Double salpingo-oöphorectomy.	Closed.	Right, retort-shaped and filled with carcinoma. Unilocular ovarian cyst. Left tube dilated.	Papillary carcinoma.	Well, 3 yrs. later.
28. Koenig.	No history.	Left.	Hysterectomy. Double salpingo-oöphorectomy.	Pelvic, peritoneal.	Left tube semi-cystic, 14x10 cm. adherent. Right hydrosalpinx. Papillary growth over uterus and adnexa.	Carcinoma, (examined by Prof. Askanaazy).	1 year. Exploratory laparotomy.
29. Boxer.	No history.	Both dilated and filled with new growth; retort-shaped. Bilateral ovarian cysts.	Carcinoma.

Conclusions.—Primary carcinoma of the tube, while not common, is not as rare as has been supposed, and its possibility must be considered when a tumor lateral to the uterus is present. There have been four such cases in the Gynecological Department of The Johns Hopkins Hospital.

Definite symptoms are not regularly associated with the tumor, but one or more of the following are usually present: a watery, often blood-tinged, vaginal discharge; abdominal pain and induration on one side of the uterus; often a tumor is present. The discharge may be intermittent in character. Each tube is involved an equal number of times by the growth, while in about 28 per cent of the cases both tubes are involved.

If the condition is still confined to the tube a complete operation (hysterectomy, double salpingo-oöphorectomy) should be done; otherwise only palliative measures can be employed. A careful macroscopic examination (and microscopic, if necessary,) should be made before the abdomen is closed of every tubal tumor removed. In some cases the complete operation was done at a second laparotomy after the nature of the growth was discovered.

A microscopic examination should be made of a serohemorrhagic fluid obtained from a lateral tumor by pelvic puncture. Such a tumor should be considered malignant until proven otherwise.

Primary carcinoma of the tube may be present in association with an ovarian cyst.

The tumor is of a high grade of malignancy. At onset it may be of slow growth, but recurrence is soon noted after operation. In most cases the condition has been too far advanced for permanent relief when surgical aid was sought. Only four patients are known to be well five years after operation.

One of the patients of the cases here reported was colored.*

CASE No. I.—Gyn. No. 11471. E. B., white, married, aged 58. Admitted August 15, 1904; discharged September 11, 1904.

Diagnosis.—Ovarian cyst (unilocular), left side; carcinoma of left tube.

Operation.—Salpingo-oöphorocystectomy (left).

Complaint.—Tumor in stomach.

Family History.—Negative.

Past History.—Always healthy. Menstruation normal. Menopause four years ago. Married twenty-three years; one child twenty years of age. Spontaneous birth. No miscarriages. No marked leucorrhœa.

Present Illness.—Patient noticed a tumor in the lower part of abdomen about six months ago. Since then it has been growing gradually. There has been no pain associated with the increase in the size of the abdomen. The patient has grown thinner about the face, arms and chest; feels weakened. Suffers much from shortness of breath. Bowels regular. Voids frequently, but without discomfort.

Physical Examination.—Mucous membranes, good color. No œdema about face. Lungs and heart negative. Abdomen much distended; measures 51 inches at its greatest girth. Flat note is obtained on percussion over whole abdomen. Oedema of feet and legs. No note on pelvic examination.

Operation.—(Dr. J. A. Sampson.) When the abdomen was

* No note concerning the color of the patients was made when the histories were abstracted, but I do not recall any patient other than white being recorded.

opened through a median line incision, a considerable amount of free fluid escaped. A large intraligamentary ovarian cyst was found on the left side. It was very adherent. The cyst was punctured and the contents were evacuated. The left tube and ovarian cyst were removed. The uterus was normal. Convalescence was uneventful.

Macroscopic Description.—The specimen consists of the wall of an ovarian cyst, with the tube attached. The cyst is approximately the size of a child's head, measuring 15 cm. in diameter. The outer wall is rough; in places a few adhesions are attached. At the base of the tube and parallel to it is an indistinct line of demarcation, where the peritoneum was cut to effect the removal of the tumor.

The tube is attached to the upper portion of the cyst and measures 15 cm. in length; it is slightly distended throughout the distal half, in which part it has a semi-elastic feel. The fimbriated end is closed and no communication between the tube and cyst cavity is to be made out. The ampullar portion is 2 cm. in diameter and on section is seen to be filled with a grayish, granular material which has a vegetative appearance. The growth is attached to the lower half of the inner surface of the tube. The tube wall measures 2 mm. in thickness. The cyst is unilocular and is lined with a serous-like membrane which strips off readily. No metastatic nodules are seen on the inner or outer surface of the cyst. The cyst wall is 1 cm. in thickness.

Microscopic Examination.—Under the low power, the tumor is seen to be attached to the lower part of the tube. No folds are seen in the upper part of the tube, but the epithelium is intact. Springing from the base of the tube are pedunculated carcinomatous masses. The growth is papillary.

Under the higher power, numerous papillæ, or tree-like forms, are seen sweeping into the lumen from the base. As seen from the microphotograph, the middle part is quite large and from it run long strands of connective tissue to the tips of the terminal processes. The epithelial cells in these processes are, for the most part, small columnar with an irregular ovoid nucleus. The cells are arranged in single and double rows. Karyokinetic figures are seen. There is considerable round-cell infiltration about the base of the tumor.

The wall of the tube is of normal thickness, and here and there the upper portion of the muscularis is seen to be infiltrated by the tumor.

The daughter gave the following subsequent history concerning her mother:

After leaving the hospital in 1904 patient was in quite fair health for two years, having at times, however, some abdominal pain. After two years the pain became more severe and quite constant and there was, at times, swelling of the abdomen. These symptoms gradually increased, so that during the last four months of the patient's life she was confined to her bed. Three small nodules appeared behind the left ear during the latter months of her life. There was no vaginal discharge at any time and no symptoms to indicate any malignancy of the bowel.

She died April 22, 1909.

CASE No. II.—Gyn. No. 18859. A. S., black, widow, aged 44. Admitted November 12, 1912; discharged December 6, 1912.

Diagnosis.—Chronic pelvic inflammatory disease. Carcinoma of left tube. Myomata uteri. General peritoneal carcinosis.

Operation.—Hysteromyomectomy. Double salpingo-oöphorectomy.

Complaint.—Sharp pain in left side of the abdomen. Painful urination.

Family History.—Negative.

Past History.—Health always good until present illness. Menses began at twelve; regular until eighteen months ago. Until six months ago the periods increased, the flow some months being noticed twice, occasionally small clots being passed. The flow

during this time has been more profuse and very painful. Last period, November 12; the two previous, October 13 and September 21. The flow now lasts for four days instead of eight before the present illness. Married twenty-seven years. Seven children, the oldest 25, the youngest 13. One miscarriage at 29. Profuse leucorrhœa during the past year.

Present Illness.—For two months the patient has been having sharp, lancinating pains in the lower abdomen, localized more in the left lower quadrant, occasionally radiating to the pelvis. The pains have become more severe during the past month. Micturition has been painful for the past four weeks, associated with increased frequency, the patient voiding at times every five minutes. Pollakiuria worse at night. The bowels are constipated. No nausea, vomiting, or elevation of temperature. The patient has lost 20 pounds in the last two months.

Physical Examination.—The patient is a moderately well-nourished negress. Mucous membranes, fair color. Cervical, axillary and inguinal glands readily palpable. Heart, normal. Numerous fine râles heard throughout the bases of the lungs. Abdomen, symmetrical. Respiratory movements, normal. Wall, pendulous. The patient complains of pain when slight pressure is made over the lower half of abdomen, especially in the left quadrant. No masses are made out. Liver dullness normal. Spleen not felt.

Pelvic Examination.—There is a slight bloody discharge from the vagina. The cervix is lacerated. The fundus is enlarged to about twice the normal size; movements limited. A hard nodular mass, approximately 8 cm. in diameter, is felt attached to the fundus. The left tube and ovary cannot be differentiated in an inflammatory mass the size of one's fist and there are nodular masses felt throughout the pelvis. The right tube and ovary are slightly adherent. There is a great deal of tenderness in the fornices. Hemoglobin, 65 per cent.

Diagnosis.—Myoma uteri, chronic pelvic inflammatory disease.

Operation (Dr. C. W. Vest).—The abdomen was opened through a mid-line incision. The omentum was studded with pearly white nodules, varying in size from 2 mm. to 2 cm. in diameter. When the pelvis was exposed, the fundus with the left tube and ovary was bound up in a dense covering of adhesions. The right tube and ovary were slightly adherent. There was an interstitial myoma, 8 cm. in diameter, in the fundus. The adhesions about the left tube and ovary were released and these structures were delivered into the incision. The tube was markedly dilated. The fimbriated extremity was open; out of it projected a portion of the carcinomatous mass. The uterus and adnexa were removed by supravaginal hysterectomy. In order to obtain more room and facilitate the removal of the mass in the left half of the pelvis, the bisection operation was done, the right half of the uterus with the corresponding tube and ovary being removed first. Had the growth been confined to the tube the uterus and adnexa would have been removed together. The adherent tumor mass was taken out to give temporary relief from the severe pelvic pain. The liver was normal in size, but four metastatic nodules, the largest of which was approximately 3 cm. in diameter, were made out on its convex surface. The patient left the hospital on the 22d day in good condition.

Six weeks later she had symptoms of recurrence. There was no further enlargement of the cervical, axillary or inguinal glands. She died May 17, 1913.

Macroscopic Description.—The specimen consists of the uterus and adnexa. The uterus has been removed by bisection (supravaginal).

To each half of the uterus is attached the corresponding tube and ovary. The left half of the uterus measures 7 cm. in length. Its peritoneal covering is smooth over the anterior surface and fundus, but posteriorly is covered with dense, fibrous, shaggy adhesions. An interstitial myoma in the posterior portion of the uterus has been divided in the operation, the smaller part being attached to the left uterine half. The myoma is firm and has the usual characteristic appearance. The uterine wall is otherwise

normal. It is 2 cm. in thickness. The uterine cavity measures 5 cm. in length. The endometrium is normal in appearance.

The left tube is markedly distended and rounded throughout the middle and outer parts. The fimbriated extremity is closed. It measures 13 cm. in length; 3 cm. in diameter in its middle portion, and 4 cm. at the fimbriated extremity. The peritoneal covering is fairly smooth over the inner half of the tube, the outer half, together with the inner side, being covered with coarse fibrous shreds.

Upon section, the lumen of the tube from within $2\frac{1}{2}$ cm. of the uterine cornu to the fimbriated extremity is filled with a spongy, granular, branching growth which has a grayish-white appearance and is uniformly attached to the lining membrane of the tube. The musculature of the tube is intact and is hypertrophied. At no place is the growth seen to penetrate as deep as the outer portion of this part of the tube wall. Throughout the portion of the tube which contains the carcinoma the wall beyond the base of the growth varies in thickness from 6 to 9 mm. The uterine end of the tube beyond the growth is normal. It measures $7\frac{1}{2}$ cm. in length; is free from adhesions and the fimbriated extremity is open. On section the lumen is normal. Excepting for a small Graafian follicle cyst at the inner pole, the right ovary is normal. At the hilum between the ovary and tube, two small nodules, each the size of a pea, are implanted on the peritoneum. These nodules are firm and their cut section has a pearly-white appearance.

Accompanying the specimen is a portion of the omentum, measuring $7 \times 5 \times 1\frac{1}{2}$ cm. and of leather-like consistence throughout. Upon section, it is seen to be almost a solid mass of carcinoma.

Microscopic Examination.—Under the low power, the inner wall of the tube is seen to be the origin of an irregular, branching growth.

The musculature is thickened. Scattered throughout the specimen, a few places are seen where there is a beginning invasion of the muscle layer immediately below the margin of the growth.

The lumen is partially filled with tumor mass and detritus.

The higher power gives the papillary forms arising perpendicularly from the tube wall. Many have typical cone tree shape.

The stroma is similar to that already described. The epithelial cells of the branching processes, while of columnar shape, are slightly smaller than those of the other two cases, as are their nuclei, and are more closely arranged. For the most part they are arranged in a single layer.

The muscular layer is seen to be invaded by the growth in different places. There is marked round cell infiltration, especially in the muscle layer.

The same typical arrangement is to be seen in the omental metastases as is shown in the microphotograph. Between the end of the branching processes, masses of carcinomatous cells and detritus are found. The same picture is seen in the nodules in the right broad ligament.

The endometrium, myometrium, right tube and both ovaries are normal.

CASE No. III.—Gyn. No. 19170. A. F., white, married, aged 47. Admitted March 21, 1913; discharged April 7, 1913.

Diagnosis.—Carcinoma of left tube. General peritoneal carcinoma.

Operation.—Left salpingectomy.

Complaint.—General weakness. Swelling of the abdomen.

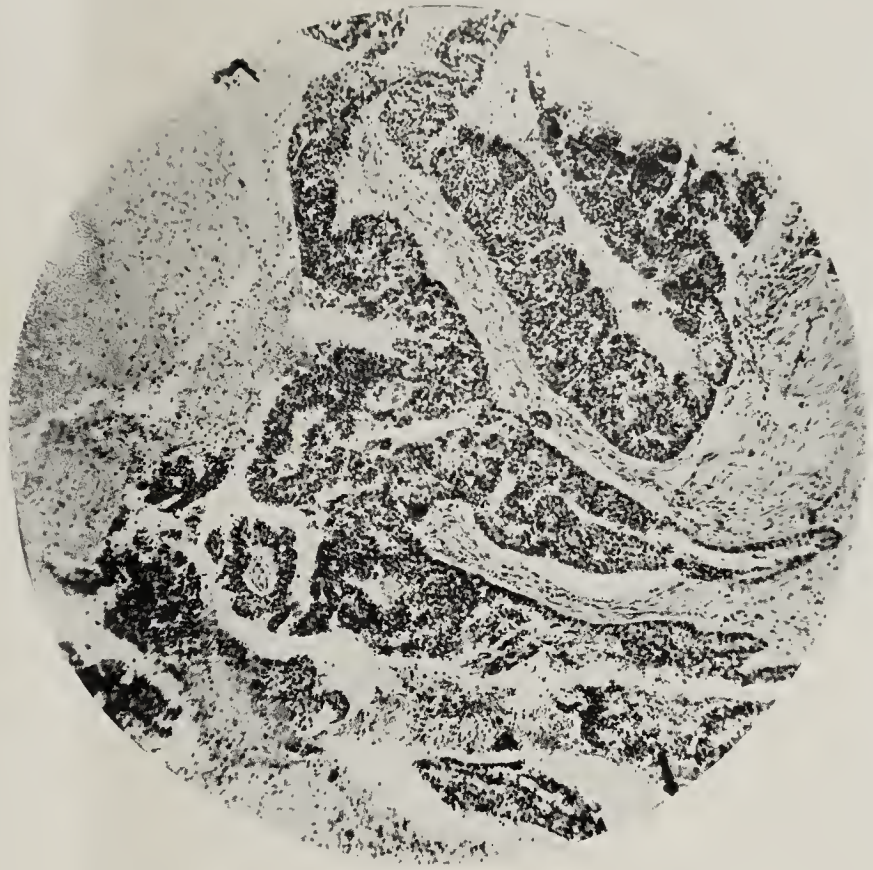
Family History.—Negative.

Past History.—The general health has always been good. Menses began at thirteen; regular every four weeks; duration, seven days; moderate flow. No pain nor intermenstrual bleeding. No leucorrhœa. Last period, January, 1913; previous one, December, 1912. The periods have been getting more scant in the past year. Married twenty-three years. No children. No miscarriages.

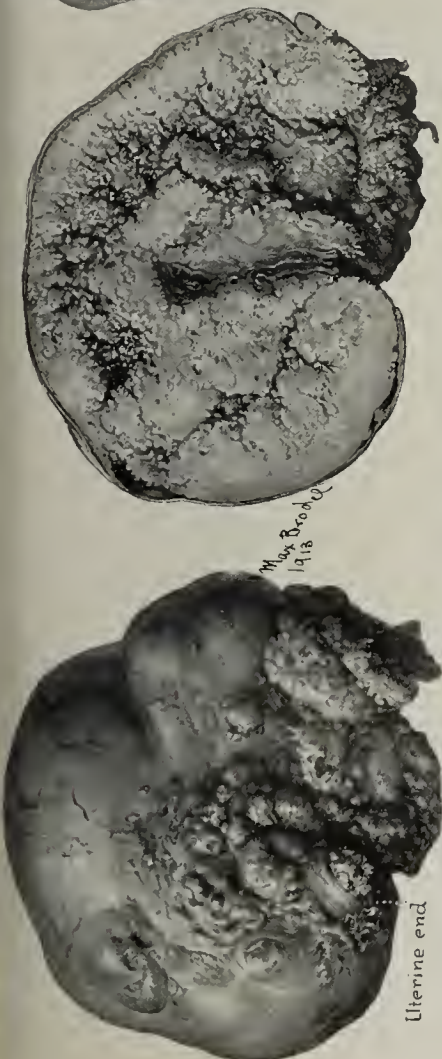
Present Illness.—About seven months before admission, patient noticed a fullness in the abdomen. The swelling has gradually



CASE No. II.—Gyn. No. 18859. Primary carcinoma of left tube. Metastases to omentum, base of right ovary and throughout the peritoneal cavity. Tube wall thickened. On account of the left-sided structures being densely adherent to the lateral wall of the pelvis and in the cul-de-sac the hysterectomy was done by the bisection method. Myoma in posterior wall of uterus.



CASE No. II.—No. 18859 (a). Papillary or finger-like processes extending into the tube lumen which is seen to contain fragments of the growth and detritus.

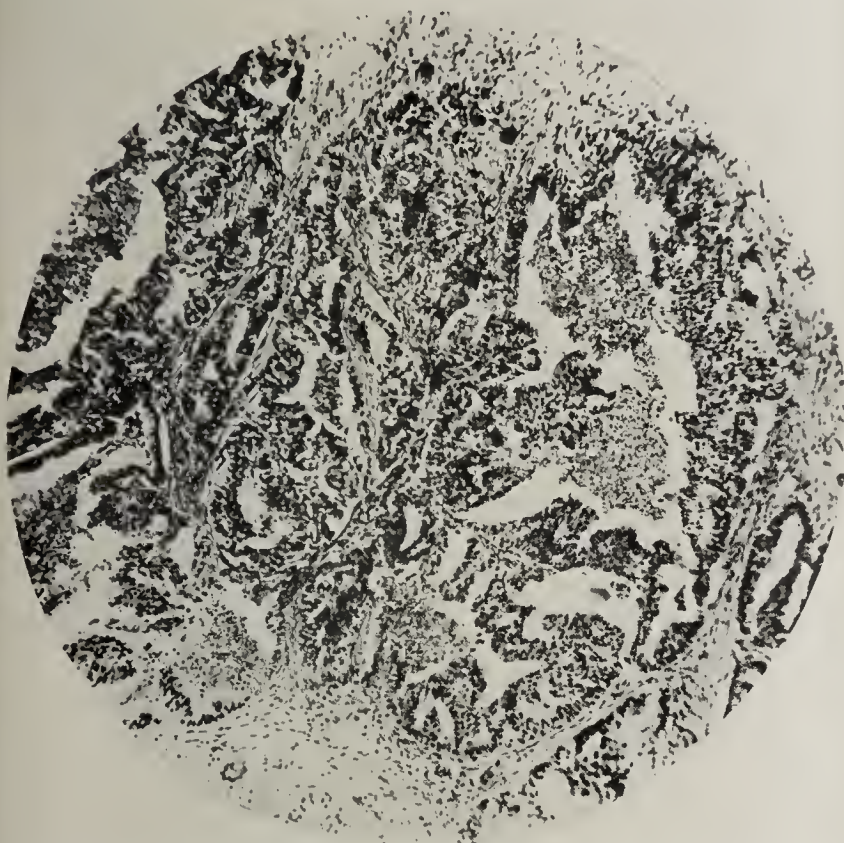


CASE No. III.—Gyn. No. 19170. (a) Primary carcinoma of left tube. The growth distends the tube. The fimbriated end is open. (b) Longitudinal section showing carcinomatous mass, the central portion of which has softened and has been partially expelled. Tube wall thin.

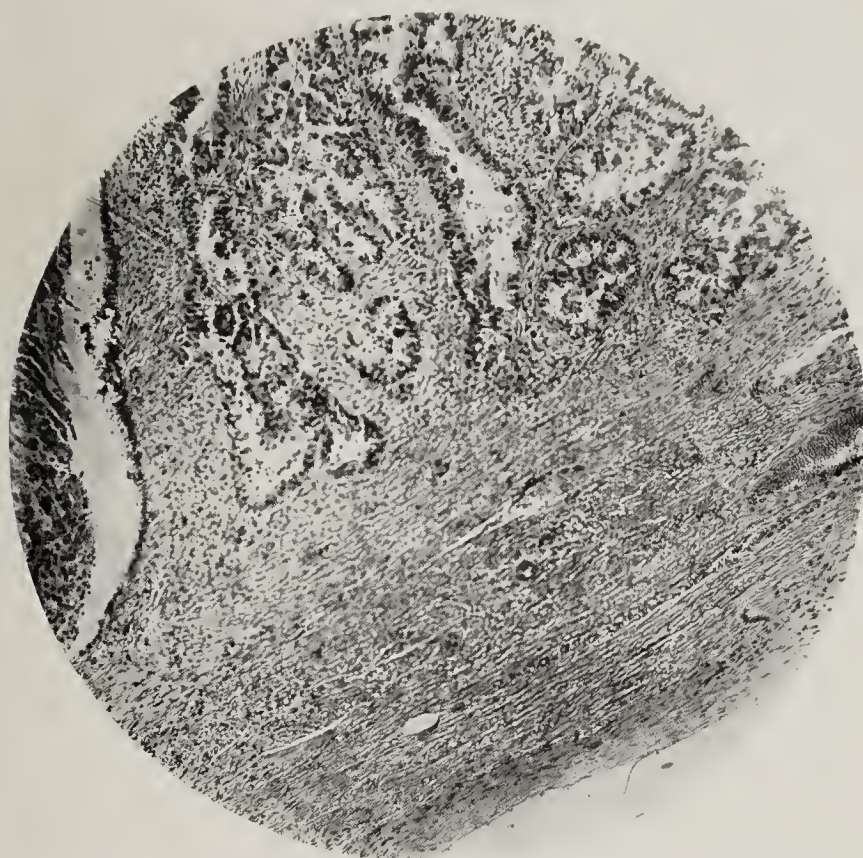


CASE No. I.—Gyn. No. 11471. Primary tubal carcinoma associated with an intraligamentary ovarian cyst. The tube is only slightly enlarged over normal.

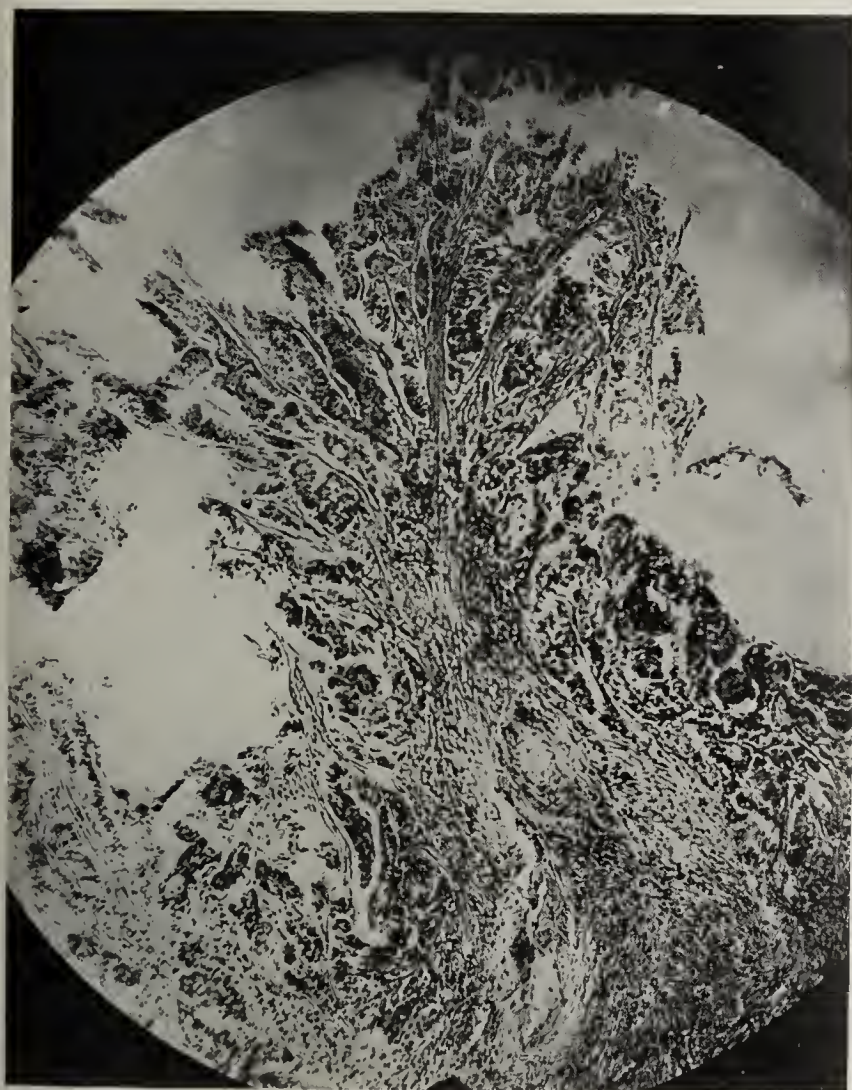
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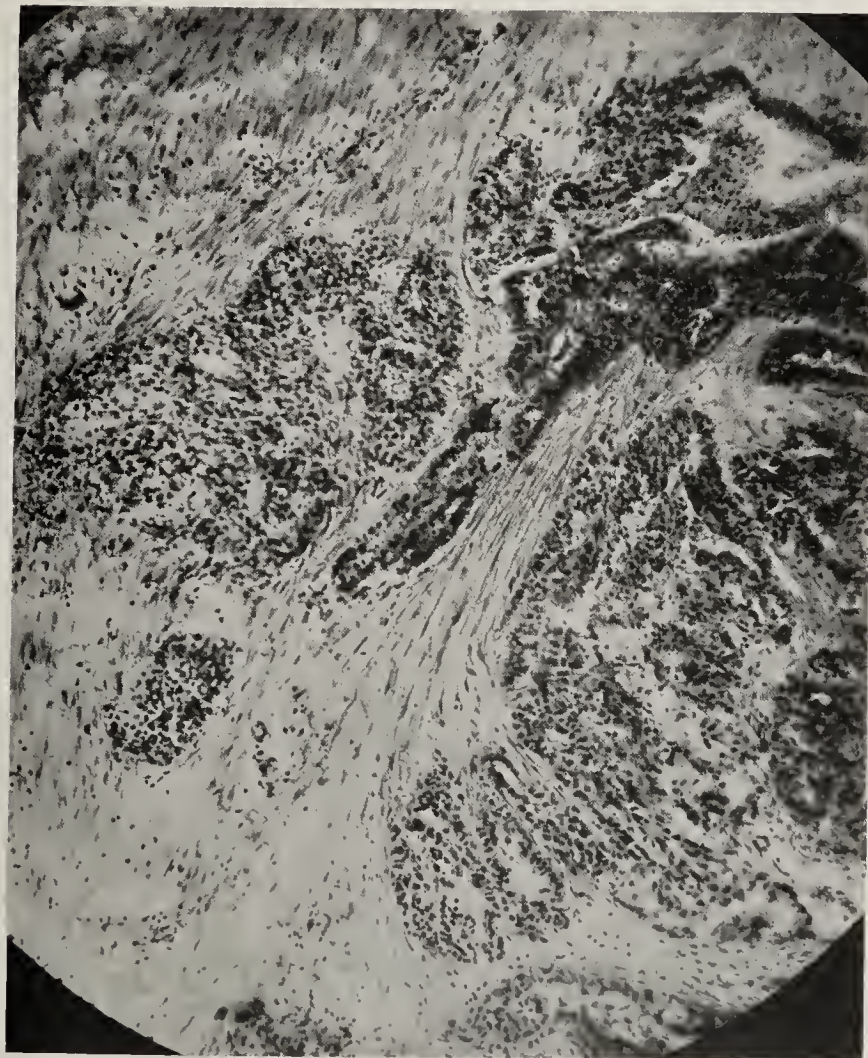
CASE No. II.—No. 18859 (c). The characteristic arrangement of the primary growth is seen in the omental metastases.



CASE No. III.—No. 19170. Origin of typical branching forms. There is no invasion of the muscle structure. The entire thickness of this layer is shown.



CASE No. I.—No. 11471. Papilla arising from base of tube. The branching, tree-like arrangement of the extending processes is clearly defined.



CASE No. II.—No. 18859 (b). Section from the muscular layer of the tube showing the downward invasion of the growth.

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increased until now the abdomen is quite symmetrically distended and prominent. Three months before admission she began to complain of general weakness and loss of weight. Four weeks ago she began to have quite severe pains throughout the abdomen and legs, associated with vomiting, slight elevation of temperature and chilly sensations. This condition persisted for over a week when she came under the care of Dr. John Folk of Bridgeport, W. Va., by whom she was brought to the hospital. The general weakness is becoming more marked. The bowels have been constipated for the past four months. No bladder symptoms nor metrorrhagia.

Physical Examination.—The patient is a fairly well-nourished woman. Mucous membranes, slightly pale. Heart, normal. The percussion note is flat below the sixth dorsal spine, extending around to the left anterior axillary line to the fourth interspace. The breath sounds in this area are of a blowing broncho-vesicular type and are accompanied by a few fine râles. The lungs otherwise are clear. The abdomen is full and rounded and there is considerable bulging of the flanks. Respiratory movements limited; no special areas of tenderness. In the left lower quadrant, an irregular nodular tumor, approximately the size of one's fist, can be felt. Definite ballottement is obtained. Definite movable dullness is made out. Liver dullness, normal. Spleen not felt. The cervical and inguinal glands are palpable.

Pelvic Examination.—The outlet is marital. The cervix is low in the vault and elongated; normal in outline. The fundus is enlarged to one-half again the normal size and is immovable. To the left of the fundus a tumor approximately 14 cm. in diameter is made out. The tumor is pedunculated and attached to the uterine cornu. It is quite tense and irregular in outline. The ovary cannot be differentiated. The right tube and ovary are adherent to the posterior surface of the broad ligament.

Rectal Examination.—Negative. Hemoglobin, 70 per cent.

Diagnosis.—Ovarian carcinoma. Ascites.

Operation (Dr. C. W. Vest).—March 22. The abdomen was opened through a median line incision and approximately 1500 cc. of clear yellowish fluid were evacuated. The latter part of the fluid was of a dull brownish color. On exploration of the pelvis the left tube and ovary were found to be adherent in an enlarged mass about 12 cm. in length. The fimbriated end was closed, but upon slight pressure on the tube there was an immediate escape of tapioca-like particles from the distal end. The right ovary was normal. The left ovary was adherent to the outer portion of the tube, but was normal in size and outline. The fundus, right tube and ovary were densely bound down by adhesions and peritoneal metastases. The right tube was slightly enlarged and its fimbriated extremity patent. There were peritoneal metastases throughout the pelvis, omentum and to the lower loops of the small intestine. The liver was normal.

The patient left the ward on the eighteenth day. The incision was well healed. There was at this time some dullness in the flanks, and on vaginal examination the indurated mass throughout the pelvis could be readily made out.

To Dr. Folk I am indebted for the following statement: The patient's condition was satisfactory and she was comfortable until November 1, when she became weaker. She had very little pain at any time. Death occurred December 18, 1913, nine months after operation.

Macroscopic Description.—The specimen consists of the left tube, which is markedly and quite evenly distended throughout its length and has a soft, doughy feel. It measures 15 cm. in length and 4.5 cm. in diameter at its middle portion. The peritoneum over the upper portion and sides of the tube is everywhere smooth, while about the base it is quite irregular and roughened by the presence of numerous hard, shot-like nodules. The tube is so distended with the tumor that portions of the carcinomatous mass are seen to project from both the uterine and fimbriated extremities. There is no evidence at any part that the tumor is about to break through the wall. When the tube is

opened, it is seen to be filled with a grayish white, putty-like mass which, except over a small area at the junction of the inner and middle thirds of the tube on the outer convex surface, is attached to all parts of the inner surface of the tube. In the proximal third of the tube the tumor is of uniform solid consistency; the central portion of the remaining part of the tubal growth is soft, necrotic and shows a blackish discoloration. The part of the tumor overlying this area, which is conical shaped, the larger part being at the abdominal ostium, has been expelled, giving one the impression of the core having been removed.

In several places throughout the mass the tumor is trabeculated, coarsely granular and has a cauliflower-like arrangement. The muscular layer has been compressed by the growth, so that macroscopically the peritoneum is apparently the only covering of the tumor.

Microscopic Examination.—The wall is 3 mm. in thickness and is of quite uniform evenness throughout. Under the low power the musculature has the appearance of being pressed against the outer covering and has not been invaded at any point by the new growth. No normal tubal folds are seen. Arising from the inner side of the musculature, throughout the length of the section, are numerous papillary finger-like processes. Each one is seen to be made up of a central stroma portion, which has an epithelial covering. Although no definite form is to be made out, there is to each papilla a pseudo-tree-like arrangement.

From the sides of the lower part of a papilla a few projecting forms are given off, but it is throughout the upper part of the process that it is seen to divide into a cluster of smaller branches. Groups of the different terminal dendritic processes are in places massed together and apparently interlock. Although the base of each process is broader than the pedicle, the decrease in size is gradual until the larger branches are given off.

The central portion or stroma of the pedicle and larger branches make up the larger part of the structure. However, as the tube lumen is approached the papillary divisions are more numerous. In this portion of the growth there is a small amount of the central supporting structure and a large increase in the epithelial elements. Necrotic material is seen in the lumen.

Under the higher power, the lateral and end processes are seen to terminate in innumerable fine finger-like processes, which are usually interwoven with similar processes from many neighboring larger branches.

The cells covering the pedicle and larger divisions are large, elongated, and in places columnar. They are arranged in layers of two to four rows. The nuclei are large, round or ovoid and fill the lower half or two-thirds of the cell. The nucleoli are uniformly present. The cells about the terminal processes are approximately the size of those just described, but are arranged in single or double rows, usually the former. Karyokinetic figures are seen through the section. Numerous polymorphonuclear cells are seen as the lumen is approached.

The stroma is composed of long spindle shaped cells whose nuclei are oblong and stain deeply with hemotoxylin. There is considerable round cell infiltration throughout.

The cases here reported are from the service of Prof. Howard A. Kelly, whom I desire to thank for the privilege of placing them on record and for his assistance so generously extended to me.

To Dr. Thomas S. Cullen I wish to express my indebtedness and appreciation for his numerous suggestions and interest.

I wish also to thank Mr. Max Brödel for his drawings.

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THE NORMAL DIFFERENTIAL LEUCOCYTE COUNT.*

By SYDNEY R. MILLER, M. D.

(From the Clinical Laboratory of the Johns Hopkins Hospital.)

1. INTRODUCTION.

In 1911 Bunting¹ reported the results obtained in making differential leucocyte counts with Wright's stain on 25 normal individuals in the third decade of life. His figures differed from those almost universally accepted as the normal standard, especially in the low average percentage of polymorpho-nuclear neutrophilic leucocytes obtained and the correspondingly higher values for the mononuclear cells. These figures are well seen in Table 1, the figures of which are compiled from the most recent text books on clinical diagnosis and hematology.

TABLE 1.—AVERAGE PERCENTAGE VALUES OF LEUCOCYTES IN NORMAL BLOOD.

Author.	P. M. N.	P. M. E.	P. M. B.	S. M.	L. M.	T.
1. Pappenheim	70-75	2-4	0-1	20-22	2....6	
2. Türk	70-75	2-4	.1-.5	22-25	1 1-4	
3. { Sahli	70-72	2-4	.5	22-25	1	1-4
Emerson						
Ehrlich						
4. Morawitz	65-75	2-4	.5	20	5....7	
5. Webster.....	65-75	2-4	.5	20-25	3....5	
6. Wood.....	65-75	2-4	.5	22-25	1 2-4	
7. Krause.....	65-70	2-3	.5	22-25	3....5	
8. Naegeli.....	65-70	2-4	.5	22-25	3....5	
9. Brugsch & S....	65-70	2-4	.5	20-25	3....5	
10. Morris.....	65-70	2-4	.5	22-25	3....5	
11. Cabot.....	60-70	.5-4	.1-.5	20-40	1...10	
12. Simon.....	60-70	1-4	.2-1	20-30	1....6	
13. Bunting	50-60	.8-4	.4-1.8	30-40	.6-2 6-8	

It is at once obvious from these figures that most observers still cling to the standards established in 1898, by Ehrlich, on counts made in Germany, and by the use of the stain that bears his name. These figures, moreover, give the impression that the individual cell values vary only within the designated

limits, and that diagnostic conclusions may be safely drawn from slight variations from them. It is obvious that the gap between Ehrlich's and Bunting's figures is wide enough to make the interpretation of many leucocyte counts a matter of considerable speculation. Bunting found no neutrophile count as high as the Ehrlich minimum; "80% of the counts are lower than the minimum accepted by the majority of authors. On the other hand, the lymphocytes are above the maximum of the majority of the text books counts and the transitionals are also on the upper margin of the accepted normal. The other elements do not vary much from the usual figures."

Bunting briefly discusses the factors to which these variations may be attributed, such as the persistence of the lymphoid activity of adolescence, into the third decade, the tendency of the Wisconsin climate to cause chronic respiratory catarrh, and the use of a Romanowsky stain instead of the Ehrlich; but counts made upon older people, attempts to detect seasonable variations, and comparative studies made with the two stains failed to show the influence of any of these factors. The present report deals with the results obtained in an attempt to verify Bunting's work.

2. MATERIAL AND METHODS EMPLOYED.

As part of the routine blood work in the course in Clinical Microscopy, it is required of each third-year student that he first learn how to make blood smears. These smears are not acceptable unless they show relatively large areas wherein each cell is separate from every other one; each student proves for himself that this necessary evenness of distribution is secured only by the use of glassware carefully cleaned and polished. A technique is gradually acquired in the application of Ehrlich's and Wilson's stains. The student then makes differential counts on films, stained by each method, which have passed inspection by an instructor; 250 cells are counted on each

* Reported before the Johns Hopkins Hospital Medical Society, May 18, 1914.

smear, and from the percentages thus obtained are calculated the absolute values of the various leucocytes per cubic millimeter of blood as based on the student's total white blood count. These results, and the preparations from which they were obtained, are collected for final approval.

For the purpose of this study the stained films submitted by 50 students were selected at random. A differential count of 250 cells was then made by the author on each of the 100 preparations, and the results tabulated for comparison with those obtained by the students from the same slides. The analysis therefore is based upon a total of 50,000 cells.

The leucocytes were divided into the following six groups:

1. Polymorpho-nuclear neutrophilic leucocytes (P. M. N.)
2. Polymorpho-nuclear eosinophilic leucocytes (P. M. E.)
3. Polymorpho-nuclear basophilic leucocytes (P. M. B.)
4. Small mononuclears (S. M.) This group includes cells of the lymphocytic type with a relatively large deeply staining nucleus surrounded by a narrow rim of basophilic protoplasm. Cells are included here which are smaller than the average sized P. M. N. (10 μ).

5. Large mononuclears (L. M.). This includes relatively few cells of the lymphocytic type the size of or larger than a P. M. N., the true "large lymphocytes," and also cells with a large round, oval, or slightly indented nucleus, eccentrically placed and poorly stained, surrounded by a considerable amount of protoplasm, the true "large mononuclears."

6. Transitionals. These are the largest cells encountered in normal blood, with deeply notched or saddle-bag nucleus, staining somewhat more deeply than No. 5 and surrounded by abundant protoplasm. The above descriptions apply to cells stained by the Wilson method, or any other of the numerous Romanowsky modifications. With Ehrlich's triple stain the specificity of the leucocytic granulations is sharply revealed, while all cells of the non-granular type are faintly stained and may be easily overlooked, especially if the differential counts are made by artificial light.

3. ANALYSIS OF RESULTS.

The results secured in the manner above described can be appreciated best by an analysis of each cell type with reference to its average percentage value, absolute number per cubic millimeter and the group distribution of the counts.

TABLE 2.—POLYMORPHONUCLEAR NEUTROPHILIC LEUCOCYTES.

Average Values.				Distribution of Counts.					
Counts made by	Wilson Stain.		Ehrlich Stain.	Number of Counts.	Wilson Stain.		Ehrlich Stain.		Percentage Distribution of Counts.
	Percent.	Absolute Number.			Students.	Author.	Students.	Author.	
Students.....	62.196	4805	66.448	5158	Over 80%	0	0	1	.5%
Author.....	60.846	4663	64.576	4955	70-80%	9	4	17	8
Average.....	61.521	4734	65.512	5056	60-70%	27	31	21	31
					50-60%	10	9	11	11
					40-50%	3	6	0	0
					Under 40%	1	0	0	0
Averages of all counts					Totals...	50	50	50	200
63.516 Percent.									100%
4895 cells per cmm.									

These figures are interesting in several respects:

1. The averages as well as the group distribution of the counts are remarkably similar. This similarity holds good in the comparison of the counts made by one person with two stains, as well as with those similarly obtained but by numerous observers.

2. As was expected, the values obtained with Ehrlich's stain are slightly higher than those with Wilson's, though this applies practically only to the number of counts over 70%. Whether these values are real or are merely evidence of the fact that mononuclear cells were missed in these particular counts is impossible to state. Of the 100 Wilson counts, 87 lie below the Ehrlich minimum and 29 below 60%, the lowest limit given by any author save Bunting. With Ehrlich's stain 74 counts are below his minimum and 22 are lower than 60%. Of the total number of counts lying between 60 and 70%, 110 in all, exactly one-half were less than 65%; the highest count in the entire series was 82% and the lowest 33.6%, giving an arithmetical mean of 57.8%. This agrees within .8% with results recently published by Galambos,² based on a series of 100 counts made by the "Zahl-Kammer Method." In a recent study of 61 cases, von Torday³ observed variations of 42.5% to 82.5%, giving an arithmetical mean of 65.1%. Observations made by Mehrtens⁴ in California on 100 normal individuals resulted in an average of 56.5%. The possibility that some of the high counts in this series were due to the existence of colds at the time the counts were made, cannot be ruled out.

TABLE 3.—POLYMORPHONUCLEAR EOSINOPHILIC LEUCOCYTES.

Average Values.				Distribution of Counts.					
Counts made by	Wilson Stain.		Ehrlich Stain.	Number of Counts.	Wilson Stain.		Ehrlich Stain.		Percentage Distribution of Counts.
	Percent.	Absolute Number.			Students.	Author.	Students.	Author.	
Students.....	2.544	205	2.704	218	Over 5%	5	7	6	8
Author.....	2.552	214	3.012	235	4-5%	7	5	6	6
Average.....	2.548	210	2.858	226	3-4%	4	5	6	4
					2-3%	13	11	14	18
					1-2%	12	11	8	8
					Under 1%	9	11	10	6
Averages of all counts					Totals...	50	50	50	200
2.703 Percent.									100%
218 cells per cmm.									

The total average is 2.7%, despite the fact that 26 counts were over 5% reaching, in one instance, as high as 10.8%. These higher values are scarcely to be wondered at, however, in view of the relatively large number of students who come from regions in the south where parasitic infections are so prevalent. Five individuals failed to show any eosinophilic cells in either one or both of the smears examined. Of the total number of counts examined as many lie between 0-2% as between 2-4%, the figures given by 9 out of the 13 authors cited. Galambos (*loc. cit.*) observed in 65 normal individuals, variations between .48 and 10.5% with absolute values ranging from 39 to 911, while Mehrtens (*loc. cit.*) found an average of but .97%.

TABLE 4.—POLYMORPHONUCLEAR BASOPHILIC LEUCOCYTES.

Average Values.				Distribution of Counts.							
Counts made by	Wilson Stain.		Ehrlich Stain.		Number of Counts.	Wilson Stain.		Ehrlich Stain.		Total of All Counts.	Percentage Distribution of Counts.
	Percent.	Absolute Number.	Percent.	Absolute Number.		Students.	Author.	Students.	Author.		
Students.....	.448	36	.452	35	Over 1%	7	9	5	9	30	15.0%
Author.....	.624	52	.529	43	.4-1%	24	33	28	28	113	56.5%
Average.....	.536	44	.490	39	0	19	8	17	13	57	28.5%
Averages of all counts } .513 Percent. 42 cells per cmm.					Totals...	50	50	50	50	200	100%

Little comment need be made on these figures which in all respects agree with the values universally accepted. The highest figure was 2.8%. It is apparently normal for a great many individuals to find no basophilic cells in counting a total of 500 leucocytes.

TABLE 5.—SMALL MONONUCLEARS.

Average Values.				Distribution of Counts.							
Counts made by	Wilson Stain.		Ehrlich Stain.		Number of Counts.	Wilson Stain.		Ehrlich Stain.		Total of All Counts.	Percentage Distribution of Counts.
	Percent.	Absolute Number.	Percent.	Absolute Number.		Students.	Author.	Students.	Author.		
Students.....	21.39	1636	20.75	1562	Over 30%	6	7	4	4	21	10.5%
Author.....	21.07	1838	21.688	1858	25-30%	4	12	7	10	33	16.5%
Average.....	22.73	1737	21.219	1710	20-25%	17	15	15	16	63	31.5%
					10-20%	23	16	23	19	81	40.5%
					Under 10%	0	0	1	1	2	1.0%
Averages of all counts 21.97 Percent. 1724 cells per cmm.					Totals...	50	50	50	50	200	100%

Small mononuclear cells or lymphocytes are perhaps the easiest of all types to recognize, especially when stained by a Romanowsky method. In a comparative study such as this, the mononuclear elements in general furnish a fairly reliable index of the care with which the differential counts are made. It was among the non-granular cells therefore that discrepancies were expected, but found to be singularly infrequent. The total average of 21.9% tallies closely with the figures usually cited, but the wide limits of variation that a cell may show under presumably normal conditions is nowhere made more manifest than here. The highest figures with Wilson's stain were 45.2%, with Ehrlich's, 39.6%; the lowest 10.4% and 9.2% respectively. Of all the counts 41.5% are under the 20% mark and 58.5% above. Of these the majority lie between 20 and 25%. Bunting's average for the small lymphocytes alone, 23.3%, is hidden by reason of the fact that he combines in one average the sum of the averages of both small and large lymphocytes. It would seem that if it is necessary to make a separate large lymphocyte group at all, it would be wiser to report the values found for it separately.

This group, it will be recalled, includes two types of cells, namely true large mononuclears and lymphocytes the size of or larger than an average sized P. M. N. While clearly recognizing the separate existence of true large mononuclears and true large lymphocytes, there seems little to commend the practice of separating these two groups in making differential counts. True large lymphocytes normally occur in small

TABLE 6.—LARGE MONONUCLEARS.

Average Values.					Distribution of Counts.						
Counts made by	Wilson Stain.		Ehrlich Stain.		Number of Counts.	Wilson Stain.		Ehrlich Stain.		Total of All Counts.	Percentage Distribution of Counts.
	Percent.	Absolute Number.	Percent.	Absolute Number.		Students.	Author.	Students.	Author.		
Students.....	9.392	700	6.368	490	Over 15%	5	4	3	3	15	7.5%
Author.....	8.388	664	7.72	585	10-15%	15	14	4	9	42	21.0%
Average.....	8.89	682	7.04	538	5-10%	19	24	22	26	91	45.5%
					Under 5%	12	8	21	12	52	26.0%
Averages of all counts	{ 7.947 Percent. 610 cells per cmm.				Totals...	50	50	50	50	200	100%

numbers, and are frequently absent in a count of 250 cells. The arbitrary grouping of these two types of mononuclear elements employed here on the basis of a size index and not the finer shades of histological differentiation certainly minimizes confusion for the students and sacrifices none of the information to be derived from the differential counts themselves. The average, 7.9%, agrees quite closely with the sum of the averages of Bunting's large lymphocytes and large mononuclear groups, namely 10.8%. The limits of variation are again wide, ranging from 35.2% to .4%. One-fourth of the entire number of counts is less than 5%; one-half fall between 5 and 10%, and three fourths of the remainder between 10 and 15%.

TABLE 7.—TRANSITIONALS.

Average Values.					Distribution of Counts.						
Counts made by	Wilson Stain.		Ehrlich Stain.		Number of Counts.	Wilson Stain.		Ehrlich Stain.		Total of all Counts.	Percentage Distribution of Counts.
	Percent.	Absolute Number.	Percent.	Absolute Number.		Students.	Author.	Students.	Author.		
Students.....	3.572	264	2.36	158	Over 4%	10	5	2	2	19	9.5%
Author.....	3.224	245	2.48	197	2-4%	30	37	30	35	132	61.0%
Average.....	3.398	255	2.42	178	0-2%	10	8	18	13	49	24.5%
Averages of all counts } 2.884 Percent. 216 cells per cmm.					Totals...	50	50	50	50	200	100%

Probably because of the generally accepted idea that transitionals are senile forms of true large mononuclear cells, many authors group these two types together as may be seen in Table 1. There is further reason for this in that the total values for true large mononuclear and transitional cells for each individual are fairly constant, a low number of one type being usually associated with higher values for the other and vice versa. Morphologically, however, transitional cells are sufficiently distinct from all others to justify their separate grouping. Their increase assumes general significance in practically only one condition, namely, Hodgkins disease, a point particularly emphasized by Bunting.* The average of 2.8% agrees closely with those cited by Emerson, Ehrlich and Sahli, but differs quite outspokenly from Bunting's of 7.4%. Of the entire number of counts, only 19 were above 4%, with an upper limit of 12.4%. Both stains threw the majority of counts between 2 and 4%.

Since the completion of the work above described, the differential counts of the two successive classes, each of 90 students, have been subjected to analysis. The close parallelism throughout the first series between the results of the students and those

of the author made it seem unnecessary to apply similar comparative studies to the blood smears of the second and third series. Counts of 250 cells were made on each slide; in addition to the Wilson and Ehrlich smears, the students of the third series were required to make a count using Jenner's stain. The second analysis therefore was based upon a total of 450 counts representing 112,500 cells. A detailed study revealed the fact that the average values and group distribution of the various cells were practically identical with those before tabulated, even to the upper and lower limits which any type may exhibit. The net results therefore are presented in the composite tables (Tables 8, 9 and 10), which also include the values obtained in the first analysis. It will be seen that the final percentage averages, absolute numbers per cubic millimeter, and group distributions represent a total of 162,500

cells and 650 counts, made with three different stains upon 230 normal individuals in the third decade of life.

The analysis of the three composite tables (Tables 8, 9 and 10) reveals the following facts:

1. The average values for the ordinary P. M. N. as determined by three stains, including Ehrlich's, are lower than the usual standards, and the cells show limits of variation much wider than is generally believed. The figures are consistently higher with Ehrlich's stain. It is probable, however, that this may be attributed in part to the omission of mononuclear cells, particularly of the large variety; these stain faintly at best with Ehrlich's stain, suffer first in the fading of the smears, and are extremely hard to detect at all by artificial light. While it is true that the neutrophilic granules are often unstained by Romanowsky methods, the cells in question

TABLE 8.—THE AVERAGE PERCENTAGE VALUES OF THE LEUCOCYTES IN NORMAL BLOOD.

	P. M. N.			P. M. E.			P. M. B.			S. M.			L. M.			T.		
	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.
1st Series—Students.....	62.196	66.448	2.544	2.704488	.452	...	21.39	20.75	...	9.392	6.368	3.572	2.36
1st Series—Author.....	60.846	64.576	2.552	3.012624	.529	...	24.076	21.668	...	8.388	7.720	3.224	2.48
Class of 1913.....	61.54	65.82	2.49	2.605	.42	...	24.42	21.92	...	7.04	6.36	3.44	2.66
Class of 1914.....	64.49	67.51	64.51	2.66	2.78	2.79	.83	.88	.82	22.34	21.50	22.	7.46	5.91	7.59	3.25	2.38	2.59
Averages	62.268	66.088	64.51	2.561	2.774	2.79	.61	.57	.82	23.306	21.459	22.	8.07	6.589	7.59	3.371	2.47	2.59
Total average of 650 counts	64.288			2.708			.633			22.255			8.083			2.81		

TABLE 9.—THE AVERAGE ABSOLUTE NUMBERS OF THE LEUCOCYTES, PER CUBIC MM. AND TOTAL WHITE COUNTS.

	Number of Individuals.	Limits of Variation in the Leucocyte Counts.	Average of all Leucocyte Counts.	P. M. N.			P. M. E.			P. M. B.			S. M.			L. M.			T.		
				Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.	Wilson.	Ehrlich.	Jenner.
1st Series—Students....	50	5200-11,000	7400	4805	5158	205	218	...	36	35	...	1636	1562	700	490	...	264	158	...
1st Series—Author.....	50	Ditto	Ditto	4663	4955	214	235	...	52	43	...	1838	1858	664	585	...	245	197	...
Class of 1913.....	90	5000-9800	7200	4430	4739	180	204	...	36	30	...	1758	1578	506	458	...	238	191	...
Class of 1914.....	90	4600-10,200	7300	4708	4928	4710	193	202	203	61	64	59	1630	1560	1606	545	431	554	237	174	189
Total.....	280	Averages..	7300	4652	4945	4710	198	215	203	46	43	59	1723	1640	1606	606	491	554	246	180	189
			Average of all 650 Counts..	4769			205			49			1656			550			205		

TABLE 10.—THE GROUP DISTRIBUTION OF 650 DIFFERENTIAL COUNTS MADE ON 230 NORMAL INDIVIDUALS.

P. M. N.		P. M. E.		P. M. B.		S. M.		L. M.		T.	
Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.	Percentage Values.	No. of Counts.
Over 80%	4	Over 5%	74	Over 1%	137	Over 30%	57	Over 15%	18	Over 4%	79
70-80%	135	4-5%	65	.4-1%	351	25-30%	124	10-15%	101	2-4%	413
60-70%	362	3-4%	72	0	162	20-25%	243	5-10%	359	0-2%	158
50-60%	126	2-3%	207	10-20%	219	Under 5%	172
40-50%	21	1-2%	125	Under 10%	7
Under 40%	2	Under 1%	107
Total	650		650		650		650		650		650

rarely fail of recognition by reason of the shape of their deeply stained nuclei. Of the total number of counts with all stains lying between 60 and 70%, slightly more than one-half were under 65%.

2. The eosinophiles and basophiles differed scarcely at all from the usual normal values.

3. For the small mononuclear cells practically the same figures were found as those given by most authors. The total average agrees within 1% of that observed by Bunting for the small lymphocytes alone. With all stains the cells show a considerably wider range than is usually taught, and as one is led to suppose by the figures generally given. The values are slightly lower with Ehrlich's stain.

4. The arbitrary group of large mononuclears including, as has been stated, two types of cells, shows an average higher than that usually cited, namely 8.08%. Bunting's figure, 1.6% represents probably the prevalence of the true large mononuclear cells. The total of his averages for the lymphocytes, both large and small, and large mononuclears, is 34.7%; that in this series, 30.3%.

5. Finally as regards the transitional cells, it is evident that the great majority of the counts with all stains lie between 2 and 4%, the values again tending to be somewhat lower with Ehrlich's stain. The average for the entire series is considerably lower than Bunting's.

6. As regards the relative values of the three stains used, the following points may be cited:

a. Ehrlich's stain is a good granular and poor nuclear stain, and tends to give higher values for the P. M. N. and lower figures for the mononuclear elements.

b. Wilson's stain is a poorer granular and a better nuclear stain than Ehrlich's and gives therefore figures somewhat the reverse of (a).

c. Jenner's stain is a better granular stain than Wilson's and a better nuclear stain than Ehrlich's. The values obtained with this stain therefore tend to lie between those of the other two.

4. GENERAL DISCUSSION.

It is rather singular that so few studies of the normal blood picture have been made since the pioneer investigations of Ehrlich and Einhorn. The matter is one of great importance, however, especially since slight quantitative changes in the differential formula are constantly being cited as possessing diagnostic value in a great number of conditions. Particularly is this true with reference to the mononuclear elements. Their increase is regarded by many as of significance in tuberculosis, typhoid fever, measles, mumps, lues, pellagra, malaria, scurvy, Grave's disease, myxoedema, tabes dorsalis, achylia gastrica, dementia præcox, Addison's disease and a host of others. But it is imperative to know within what limits a cell may reasonably vary under normal conditions in order to be able to interpret its abnormal increase or decrease. The older values for the non-granular elements were determined by staining methods which did not bring out the mononuclear cells as do more modern ones. Moreover, in all likelihood there exist

quantitative differences in the leucocytic formula of normal individuals due to a number of local conditions, such as altitude, climate, humidity, and so on, as well as purely individual factors. Baer and Engelsmann,⁶ for instance, confirm the work of Staubeli⁷ concerning the leucocytic formula in higher altitudes, all agreeing that whereas the large mononuclears and transitionals show no change from their lowland values, the lymphocytes undergo an absolute and percentage increase at the expense of the neutrophilic cells. During a number of purely physiological processes such as exercise, sleep and during the digestion particularly of fats and carbohydrates, numerous observations have shown the tendency for mononuclear elements to be increased. A great number of clinical observations have tended to prove that the influence of various internal secretions tend to raise the mononuclear content of the blood, especially in those individuals who show a predominance of vagotonic symptoms. Galambos (*loc. cit.*), in the study of 100 normal individuals, found a total average of the mononuclear elements of 39.5% with variations from 18 to 67% of the total white count. He goes so far as to state that there may be as many lymphocytes in health as there are in certain diseases, leukemia excepted. von Torday (*loc. cit.*), in 61 cases, saw variations of 13 to 40.4%; and Mehrrens (*loc. cit.*), in 100 cases studied in California, secured an average of 37.45%. As the result of the examination of 110 cases, Huhle⁸ concludes that only counts which repeatedly show a lymphocytosis of over 35 to 40% are of any importance. That local climatic factors and other physical forces not exactly known exert a determinative influence upon the leucocytic formula is nowhere better shown than in the basin of the Great Lakes, in this country, where not only in human individuals, but throughout the animal kingdom, there is a tendency to lymph-adenoid hyperplasia manifested during life in the blood and frequently in the glandular system, and at autopsy by the finding of enlarged glands and spleens which average a greater weight than in other sections of the country.

Even the total white count is subject to a wider variation than is generally conceived. The figures in this series shown in Table 9, are in accord with those of Galambos (*loc. cit.*) who finds an average of 7413 with extremes lying between 3500 and 12,500. All the high counts in this series, with one exception, were associated with values for the P. M. N. below 65%. Galambos was able to show that in the same individual, on the same day, the leucocytes may vary 100%. He found no striking difference between the two sexes, nor was he able to disclose any marked or constant post-prandial leucytosis. Where one did occur, the mononuclear elements were most affected.

5. CONCLUSIONS.

From the work cited and results herewith recorded, the following conclusions may be drawn.

1. The total leucocyte count and differential formula in normal individuals are subject to relatively wide variations, which must be considered in the interpretation of studies made upon the bloods of individuals presumably suffering from abnormal conditions.

2. The interpretation of any differential count should be based upon:

a. A knowledge of that particular individual's normal blood picture, when possible.

b. The average values for the locality in which that individual resides.

c. A consideration of those factors peculiar to the individual which might modify that particular blood.

3. Differential leucocyte counts should always be reported in terms both of percentage and absolute numbers per cubic millimeter, and in all cases, where possible, more than one differential count should be made, especially in borderline cases in which slight changes are to be regarded as of diagnostic or prognostic value.

4. The tendency to ascribe a diagnostic value to lympho-

cytosis is probably overdone. Only when the mononuclear elements constantly exceed the average percentage, absolute values and upper limits of variation (35-40%) for the community and when all modifying factors are considered, should one attempt to draw valuable conclusions from the figures obtained.

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THE QUARTER CENTENNIAL ANNIVERSARY OF THE OPENING OF THE JOHNS HOPKINS HOSPITAL AND THE TWENTY-FIRST ANNIVERSARY OF THE OPENING OF THE MEDICAL SCHOOL

Will be observed by appropriate exercises beginning October 5, 1914, and continuing during the week.

The exercises upon Monday, October 5, 9.30 a. m. to 12 m., are to be especially arranged for by the Training School for Nurses and will be announced later.

Upon Monday at 3.00 p. m., the formal opening meeting will be held at the Lyric, Judge Henry D. Harlan, President of the Board of Trustees of the Johns Hopkins Hospital will preside, and there will be addresses by President-Elect F. J. Goodnow, Dr. Wm. H. Welch, Dr. Henry M. Hurd, Miss M. Adelaide Nutting and Dr. Winford H. Smith.

In the evening there will be dinners of the former Medical Officers of the Hospital and of the Alumnae of the Training School for Nurses.

Upon Tuesday, October 6, 9.30 a. m. until 12 m., papers upon medicine by former members of the staff will be presented in the Medical Amphitheatre. Gynecological operations in the Surgical Amphitheatre 10 a. m. until 1 p. m. Papers and demonstration by members of the Obstetrical Staff in the Surgical Lecture Room from 12 m. to 1 p. m.

Luncheon at the Hospital from 1 to 2.30 p. m.

At 2.30 p. m. there will be visits to the Harriet Lane Home with Dr. Howland, Professor of Pediatrics, and to the Henry Phipps Psychiatric Clinic with Prof. Adolf Meyer, Professor of Psychiatry.

A demonstration of nurses' work in the Medical Amphitheatre from 4 to 5 p. m.

From 4.30 to 5.30 a lecture on the Herter Foundation by Dr. Thomas Lewis of London.

A dinner in the evening by the Alumni of the Medical School.

Wednesday, October 7, from 9.30 a. m. to 12 m., surgical operations in the Surgical Amphitheatre. From 11 a. m. to 1 p. m. Urological Surgery in the Surgical Amphitheatre.

1 p. m., Luncheon.

At 2.30 p. m. visits to the Medical Laboratories.

4.30 p. m. Dedication of the Hewetson Medallion and a Tablet to Deceased Residents.

On Thursday, October 8, 9.30 a. m. to 12 m. papers on Pathology in the Medical Amphitheatre. The entire forenoon will be given over to papers by former members of the Pathological Staff.

1 to 2.30 p. m. Luncheon.

4:30 p. m., second Herter Lecture by Dr. Lewis.

In the evening, Class Dinners.

Third Herter Lecture will be given on Friday, October 9.

During the Anniversary Week laboratory demonstrations will be given in the laboratories of the Medical School as follows:

In the Anatomical Laboratory, By Prof. Mall and the Anatomical Staff.

In the Physiological Laboratory, By Prof. Howell and the Physiological Staff.

In the Pharmacological Laboratory, By Prof. Abel and the Pharmacological Staff.

The exact dates and hours of such demonstrations will be announced in the final program.

PROGRAMME

MONDAY	TUESDAY	WEDNESDAY	THURSDAY
Nurses' Day	9.30-12 Medicine (Medical Amphitheatre) 10-1 Gynecology (Surgical Amphitheatre) 12-1 Obstetrics (Surgical Lecture Room)	9.30-12 Surgery (Surgical Amphitheatre) 11-1 Urological Surgery (Surgical Amphitheatre)	9.30-12 Pathology (Medical Amphitheatre)
	Luncheon	Luncheon	Luncheon
Opening Meeting (The Lyric) 3.00 Judge Henry D. Harlan, presiding Addresses: Pres. F. J. Goodnow Dr. Henry M. Hurd Dr. Wm. H. Welch Miss Adelaide Nutting Dr. W. H. Smith Music	2.30 Pediatrics Dr. Howland 2.30 Psychopathic Wards Dr. Meyer 4.30 Herter Lectures Dr. Lewis 5.00 Garden Party (Hospital Lawn)	2.30 Visits to Laboratories Drs. Abel, Howell and Mall 4.30 Dedication Medallion: Dr. Hewetson Tablet to Deceased Residents	2.30 Inspection James Buchanan Brady Urological Institute 4.30 Herter Lectures Dr. Lewis
Dinners Johns Hopkins Hospital Residents Nurses	Dinner Medical Alumni	Class Dinners	

THE HERTER LECTURES FOR 1914.

The Herter Lectures will be given in connection with the Quarter Centennial Anniversary of the Opening of The Johns Hopkins Hospital and the Twenty-first Anniversary of the Opening of the Medical Department of The Johns Hopkins University, upon Tuesday, Thursday and Friday, October 6, 8 and 9, 1914, at the Physiological Lecture Room, Monument and Washington Streets, at 4.30 p. m., by Thomas Lewis, M. D., University College, London, England.

Dr. Thomas Lewis, in charge of the heart station at University College, and Editor of *Heart*, has done important work in the study of cardiac conditions, and will present three lectures on the scientific study of the heart and its bearing on clinical medicine. He is the first clinical investigator who has filled the position of Herter Lecturer. The titles of his lectures will be announced later.

Physical
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OF THE
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6 NOV 1914

BULLETIN

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THE EXPERIMENTAL PRODUCTION OF AMŒBIC DYSENTERY BY DIRECT INOCULATION INTO THE CÆCUM.

By ANDREW WATSON SELLARDS

AND

WALTER ALBERT BAETJER.

(From the Medical Clinic of the Johns Hopkins Hospital.)

OUTLINE.

- I. Synopsis of the Usual Methods of Injection and their Results:
 1. Frequent transmission of amœbic dysentery to lower animals.
 2. Uncertainty of the result of rectal inoculation or ingestion of infective material in susceptible animals:
 - A. 65 per cent of infections reported by Craig.
 - B. 100 per cent failures reported by Walker.
 3. Distinction between first inoculation from man to lower animals and the subpassages from one kitten to another.
 4. Failure to secure continuous subpassage of a strain by ordinary methods of inoculation.
- II. Methods of Inoculation.
 1. Explanation of failures by circumstantial conditions rather than individual non-susceptibility.
 2. Suggestion that pathogenic entamœbæ are unable to penetrate the uninjured mucosa.
 3. Failure of injections into wall of intestine.
 4. Infections following injection into lumen of cæcum.
 5. Evidence that pathogenic amœbæ can injure and penetrate the healthy mucosa.
- III. Results of Intracæcal Inoculations.
 1. High percentage of infection in the inoculation of eight strains from patients into animals and on sub-inoculation of animals.
 2. Comparatively high mortality from bacterial infections developing, usually, after several passages.

- IV. Relation of Intracæcal Inoculations to Other Methods of Injection.
 1. Occasional failure of typical strains to infect, even at height of virulence, on inoculation per rectum.
 2. Failure of atypical strains of amœbæ to parasitize in animals, after rectal inoculation.
 3. Factors bearing on explanation of higher rate of infection on intracæcal inoculation:
 - A. Anæsthesia.
 - B. Lack of tendency to expulsion of injected material.
 - C. Economy of infective material.
 - D. Avoidance of deleterious diluting agents.
 - E. Precision of the site of injection.
- V. Relation of Bacteria to Amœbæ.
 1. Possible views that:
 - A. Bacteria are beneficial for the growth of amœbæ.
 - B. That they are an indifferent factor.
 - C. That they are detrimental.
 2. Scarcity of amœbæ in animals with severe bacterial infections.
 3. Suppression of bacteria in active amœbic lesions.
- VI. Application of Intracæcal Methods of Inoculation.
 1. Propagation of strains for investigation.
 2. Diagnosis of difficult cases.
 3. Study of atypical amœbæ.
 4. Study of the constancy of morphological characteristics of amœbæ.

SYNOPSIS OF METHODS OF INOCULATION AND RESULTS.

The infection of lower animals with amœbic dysentery has been accomplished so frequently and with such typical reproduction of the principal features occurring in man that simple transference of the disease to lower animals ceases to be of special interest. Upon examining the methods of inoculation, however, it is found that the result of the injection of infective material in any individual instance is extremely uncertain. Even with the most suitable animals and with optimum infective material, there is a fairly high percentage of failures. Craig,¹ working with young kittens and with dysenteric stools, rich in trophozoites and cysts, obtained the best results by feeding material containing cysts, two-thirds of a small series of animals contracting dysentery. The most unfavorable results are reported by Walker²; three species of animals, namely, pigs, kittens and monkeys, remained persistently normal after inoculation with stools rich in amœbæ. Some of the monkeys were fed repeatedly with the cysts of *E. histolytica*, while others were fed, or injected per rectum, with dysenteric stools, in one instance the gastric juice being neutralized with magnesium oxide before feeding; in all, six monkeys were used. Two cats and a young pig were fed with cysts of the pathogenic entamœbæ, while six kittens were inoculated per rectum with trophozoites. In no instance, however, did any of these animals contract dysentery or even become parasitized. Wenyon³ reported only four failures in twelve inoculations of *E. histolytica*; two of these failures can be disregarded, however, since they occurred under very unfavorable conditions; the other two occurred in an adult cat inoculated first with material obtained directly from a patient, and later with a strain that had been passed through two kittens. With two strains of *E. coli*, and also with an unidentified strain, no infections occurred. Moreover, in the case of *E. histolytica* it is important to note that this high percentage of infections was secured by Wenyon upon subinoculation from kitten to kitten; that is, the data are based chiefly upon successive transfers in lower animals. Since there is evidence that the virulence of the entamœbæ increased upon passage from animal to animal, one must distinguish carefully between percentages based upon the infections obtained in sub-passages from kitten to kitten and the number of infections occurring in the first inoculation in lower animals.

Moreover, the results upon subinoculation have been so unsatisfactory that strains of dysentery have not ordinarily been carried through more than three or four passages in animals. In a single instance Werner⁴ succeeded in carrying a strain through five, and in a second instance, through six passages. This difficulty in propagating any individual strain of dysentery in animals has usually been ascribed to the loss of virulence of the entamœbæ. Definite evidence was obtained by us, however, that it was due, in part, to the uncertainty of the method of inoculation.

INOCULATION BY LAPAROTOMY INTO THE CÆCUM.

In any experimental work with dysentery it would be extremely desirable to obtain a method by which infection would follow with reasonable certainty upon the inoculation of virulent organisms. Very few suggestions have been offered, however, in explanation of the high percentage of animals which escape infection upon inoculation with virulent amœbæ. In general, the explanation of these failures has been referred, not to individual non-susceptibility, but rather to circumstantial factors. It has been thought by some that even virulent *E. histolytica* may frequently be unable to penetrate the uninjured mucosa of the intestine just as the protozoa and many bacteria are unable to penetrate the uninjured skin. On this basis we thought that more constant results might be obtained if the entamœbæ were injected into, or just under, the mucosa of the bowel, depending upon the resistance of the animal to take care of any bacterial invasion. Two monkeys and four young adult cats were inoculated under general anæsthesia in this way into the wall of the cæcum, the injection being made into the deeper coats of the bowel wall. The monkeys recovered promptly from the injection, no symptoms of dysentery developed, and at an exploratory laparotomy four weeks later, no ulceration could be found in the large intestine. Of the four cats, two died promptly from septicæmia, while the other two were sacrificed after two weeks, but showed no evidence of infection. This routine was abandoned and instead of inoculating into or under the mucosa, the infective material consisting of trophozoites, but apparently free from cysts, was injected into the lumen of the cæcum and the mucosa opposite the needle point was scarified and rolled with slight pressure between the thumb and fingers. The first three animals inoculated in this way developed typical bloody mucous stools containing many amœbæ after an incubation period of about one week. At autopsy, however, it was found that, in two instances, the lesions were distinctly below the lowest portion of the bowel which could possibly have been traumatized at operation. Accordingly, in the subsequent inoculations the material was injected directly into the lumen of the bowel with as little injury as possible to the mucosa. The details of the technique were as follows:

A laparotomy was done under general anæsthesia (ether) though care was taken to avoid the extremely deep narcosis resulting in sphincter relaxation and evacuation of the intestinal contents. Adult cats were selected when it was desired to secure chronic lesions but young animals, half-grown or smaller, were chosen when it was especially desirable to secure an active infection. In the first transfers from man to kittens no difficulty was experienced with bacterial infection.

As a routine the syringe was filled with the material to be inoculated before it was connected with the needle in order to have a sterile needle for puncturing the bowel; a moderately large puncture wound could be made in the gut, the syringe needle withdrawn and the peritoneum closed without further precautions. When flakes of blood and mucus were injected it was not necessary to comminute them since comparatively large pieces could be forced by moderate pressure through a medium sized needle. A considerable amount of pressure could be obtained when one person held the syringe needle firmly in position and the other attended to the injection, using preferably an asbestos packed syringe. Firm par-

¹ Craig: Parasitic Amœbæ of Man. Phila., 1911.

² Walker: Philippine J. Sc. B., 1913, VIII, 286.

³ Wenyon: J. Lond. School Trop. Med., 1912, II, 27.

⁴ Werner: Beih. z. Arch. f. Schiffs. u. Trop. Hyg., 1908, XII, 425.

ticles in the injection mass sometimes gave trouble by plugging the needle. When the material was not too viscous these particles could often be avoided by allowing them to settle out in the syringe for a few minutes, taking care to point the syringe upward during the injection so that they would gravitate away from the needle. When the material to be injected was especially troublesome, a small trocar on the syringe could be used with safety, provided the puncture wound was closed with stitches through the serosa.

No trouble from bacterial infection was experienced at any time in the inoculation of human stools into kittens. However, on subpassage from kitten to kitten there was a remarkable increase in the virulence of the accompanying bacteria. At times it became impossible to avoid peritonitis since, in some instances in young kittens, the bacteria were able to penetrate the bowel and produce peritonitis after injection per rectum. Fortunately, as the virulence of the bacteria increased, the virulence of the amœbæ also increased, so that the percentage of infections upon injection per rectum was comparatively high and it was only in the rarer instances that the animals were lost during the incubation period of the amœbæ by bacterial infection following rectal injection.

The large intestine in the cat is almost a straight tube lying practically in the mid line, the cæcum being rather rudimentary. The injections were made as a routine into the cæcum since it was supposed that the entire large bowel was susceptible to infection as in man. However, it was subsequently found that the lesions of the bowel appeared uniformly in the lower part of the rectum. The infections were taking place with such regularity that the injections into the cæcum were continued in order to give encysted amœbæ more time for germination. It is possible, of course, that the site of injection was in part responsible for the location of the lesions in the lower part of the bowel. In two instances, however, in which the injection was made a few inches above the ileo-cæcal valve, the lesions appeared as usual in the rectum and not in the cæcum. While this is only suggestive, nevertheless, we are inclined to feel that the absence of anatomical lesions in the cæcum was due, not to the site of injection, but that it was due perhaps to a natural non-susceptibility of this part of the bowel. Although the cæcum appeared to be the optimum point for routine injections, yet under special conditions one might want to consider other locations, such as the lower portion of the rectum.

The regularity with which the lesions appeared in the rectum after inoculation through the wall of the cæcum offers conclusive evidence that *E. histolytica* is able to penetrate the uninjured mucosa, or more precisely, that it is able to produce whatever injury is necessary in the healthy mucosa in order to penetrate it. The prompt healing of the puncture wound, although it was often thoroughly inoculated with amœbæ by back pressure after withdrawing the needle, and the development of the amœbic ulcers several inches lower in the bowel, were very striking. Furthermore, the scarification and maceration of the injected amœbæ into the mucosa of the intestine did not produce infection at the site of this injury.

RESULTS OF INTRACÆCAL INOCULATIONS.

The inoculations into the lumen of the cæcum gave unexpectedly favorable results. A variety of strains of amœbæ

was tested, ranging from characteristic acute cases to extremely chronic atypical forms. These cases came from areas which were widely separated geographically; namely, the United States, Central America, and the Philippines. With the exception of those animals which died from secondary causes during the first week after inoculation, there were no instances in which the injection of amœbæ failed to infect the animals. This is especially interesting since some of the patients did not show characteristic symptoms of dysentery and the amœbæ in the specimens of stool used for inoculation were often extremely scarce and atypical in morphology. Eight strains of amœbæ were tested. One of these was a very acute relapse, two were moderately acute cases occurring in Panama City, three were chronic cases of very moderate severity from the Southern States, whereas the remaining two were cases of such an atypical nature that their etiology was not clear. In the original inoculation from patients to animals, a total of ten cats was used. All contracted dysentery with numerous entamœbæ in the stools. The incubation period varied from six to ten days, in acute and chronic cases, to one month in the animals inoculated with the atypical strains. We attempted to propagate three of these strains by subinoculation through a series of animals. In the subinoculations from kitten to kitten a total of nineteen animals was used for the intracæcal injections and ten of these died of bacterial infection, either peritonitis or septicæmia, within one to five days after injection; *i. e.*, during the incubation period of the amœbæ. The majority of these deaths occurred in a large group of animals which was inoculated with one strain, at a time when it was contaminated with an especially virulent streptococcus. Of the animals which lived six days or longer, all contracted dysentery. One strain was carried through five passages by the intracæcal inoculations and subsequently through six additional passages by inoculation per rectum; another through three passages; and a third was lost in the second passage by bacterial peritonitis. The positive results after increasing the virulence by passage are of less importance than the infections occurring in the first transfers from patients.

RELATION OF INTRACÆCAL INOCULATIONS TO OTHER METHODS OF INJECTION.

The general relationship of the intracæcal injections to other methods seems to be fairly clear. We made no attempt to secure any statistical data in regard to the comparative value of different methods. Two procedures for infecting animals have long been in common use; namely, the injection per rectum and feeding experiments. Neither of these procedures has consistently given more than 50% of infections, even under optimum conditions. Moreover, the results of inoculation have been so uncertain that it has not been possible to secure continuous propagation of amœbæ or to compare various strains of *E. histolytica* in regard to their pathogenesis or the fixity of their morphological characteristics. It is evident that it would be very desirable to have a method for studying the pathogenesis of unusual types of amœbæ, or even for diagnosis in suspected cases during the interim between

attacks. Although we have made no parallel experiments with exact controls, our experience with several strains of dysentery appears conclusive of the greater certainty of infection following intracæcal injections as compared with other methods. The following observations seem even more crucial than duplicate experiments under the same conditions. In the subinoculation of a typical strain of dysentery by rectal tube only two failures resulted in a total of eighteen animals.⁵ These occurred, however, under conditions which illustrate well the uncertainty of injections per rectum. Plenty of material rich in trophozoites and cysts was used for these injections. The two failures occurred in kittens, one of which was three-fourths grown and the other one-eighth grown. Three other one-eighth-grown kittens of this same litter were successfully inoculated at the same time. Moreover, at the time that the second failure occurred, the strain had just been passed through a series of six kittens and its virulence had increased markedly, the incubation period being shortened from six to three days. That the virulence had not died out suddenly was shown by the infection of three other kittens at the same time, and the subsequent passage of this strain through a series of four animals without loss of virulence.

In contrast with these two failures, there was no instance in which the intracæcal injections failed to produce dysentery, even though the cases studied were extremely mild and the amœbæ in the specimens available for inoculation were extremely scanty and atypical in morphology.⁶ The best illustration of this occurred in a patient with a history of diarrhœa of several years duration, without blood and with practically no mucus in the stool and without periods of intermission in symptoms. After purging with salts, microscopical examination showed three or four trophozoites and one four-nucleated cyst was found after looking over several coverslip preparations. The trophozoites were atypical in morphology and there were numerous uninucleated cells present which histologically might very well have been cysts of the limax group. Cultures for the limax group remained entirely negative. Inoculation of a rather large quantity of stool of this patient produced the same type of diarrhœa in a kitten, after an incubation period of one month, that characterized the symptoms in the patient. Subinoculations were readily secured. A second case was obtained with a similar clinical history. No

motile amœbæ and no four-nucleated cysts were found microscopically, but the inoculation intracæcally of the stool of this patient produced a watery diarrhœa after an incubation period of one month, with the presence of moderate numbers of amœbæ, especially after purging.

The most favorable results with injections per rectum have been reported by Wenyon.^{1-c} Five strains of amœbæ were studied; two of these were typical pathogenic *E. histolytica*, one of which was inoculated successfully into two animals, the other failing to infect an adult cat. The other three strains produced the same type of diarrhœa in a kitten, after an incubation period of one month, that characterized the symptoms but all three of these non-pathogenic strains failed to parasitize cats. In subinoculations with the strain of *E. histolytica*, ten cats in all were used; only three negative results occurred and two of these were in animals inoculated with material from the fourth passage which was obtained several hours post mortem, most of the amœbæ being dead at the time of injection.

The result reported by other authors and our own experience have lead us to feel definitely that the intracæcal inoculation gives a better opportunity for infection than feeding experiments or rectal tube injections, and that it is distinctly preferable to some of the older procedures in which, after injection per rectum, the anus was sutured to avoid loss of the infective material.

The exact explanation of the favorable results after intracæcal inoculation probably depends upon a number of minor factors. At first glance it would seem that precisely the same result could be accomplished either by inoculation into the cæcum directly through its wall or by the use of a high rectal tube. Upon closer examination it will be seen that there are several minor points of difference. In the first place the general anæsthesia which is required is probably an advantage. It hardly seems possible that anæsthesia of a few minutes duration could have any appreciable effect on lowering the resistance of the animals. Its chief value in aiding infection probably lies in keeping the intestinal tract quiet and thus avoiding the prompt expulsion of the injected material. The animals after operation frequently remained as long as one or two days without defecating and then only formed stools were passed. Another point of definite significance is the economy of material which is permitted. It frequently happens that only a few flakes of blood and mucus rich in amœbæ and comparatively free from faecal material, as in specimens obtained by the passage of a rectal tube, may be available. By an intracæcal injection this can be introduced directly into the lumen of the bowel with a minimum loss of material in the injection apparatus and often without the use of any diluting agents; at most only a minimum quantity of diluting fluid is necessary. This is a distinct advantage, for it is not possible to imitate artificially the exact composition of the menstruum in which the amœbæ are found, and they are rather better preserved in the medium in which they occur than in artificial mixtures of salt solutions. Lastly, the precision with which the site of injection can be selected is a factor to be considered.

⁵ Certain minor precautions were observed throughout these inoculations. In the first place, the animals were always anæsthetized. This not only made them much easier to handle, but it prevented, in a large measure, the tendency to evacuation immediately after injection. A very small rectal tube was used, the smallest size catheter, cut to a convenient length and inserted rather high in the bowel. The infective material was injected with a syringe, using as little diluting fluid as feasible. After the injection, the catheter was compressed as it was withdrawn in order to distribute the material remaining in it throughout the bowel. A distinctly atypical case of dysentery inoculated per rectum with these precautions into a kitten produced a single acute attack.

⁶ In one instance a negative result followed the inoculation of a specimen which showed no amœbæ after thorough microscopic examination.

With a rectal tube, one can only distinguish between a low, high and medium position. In view of the constancy with which the lesions appear in the lower rectum, it is quite possible that material containing only trophozoites could be inoculated to best advantage in this region. Moreover, with a rectal tube one cannot tell whether the blood and mucus is being introduced directly into a faecal mass or against the wall of the intestine. With the intracæcal inoculation, the material can at least be deposited against the mucosa, avoiding an injection into definite faecal masses.

RELATION OF THE AMŒBÆ AND BACTERIA.

The question of the avoidance of faecal masses during injection brings up for consideration the nature of the relationship of the amœbæ and bacteria to each other. All possible views have been suggested. It is almost an open question as to whether the bacteria are beneficial or detrimental to the growth of amœbæ, though possibly they constitute an indifferent factor. Perhaps the conditions vary with different species of bacteria, but it seems fairly certain that the bacteria seldom, if ever, constitute an indifferent factor. In many instances it was observed that the amœbæ were absent or very scarce in animals in which there was extensive bacterial infection such as peritonitis or septicæmia. Moreover, in the later stages of amœbic infection, the organisms frequently became much less numerous in those instances in which a profuse bacterial enteritis developed. Likewise, the bacteria were often extremely scanty in the profuse discharges of blood and mucus in the early stages of dysentery. Similarly, in an amœbic abscess of the liver, the bacteria, though present, were not sufficiently abundant to be identified by microscopical examination and could only be demonstrated by cultures. It would seem plausible to consider that bacteria, if present, must be in a large measure suppressed, since the unrestricted growth of bacteria is detrimental to the entamœbæ. It is more than probable that certain bacteria, in limited numbers, may serve as food for amœbæ; that bacteria are not essential is also shown by the occurrence of liver abscesses which are bacterially sterile. On this basis then, it would seem almost impossible for the pathogenic entamœbæ to grow in the normal faecal contents of the bowel, but they could best secure their foothold on the surface of the mucosa. Of course, in active dysentery, when the faecal matter is replaced by blood, mucus, and epithelial sloughs it would be quite conceivable that the amœbæ could multiply in this material in the lumen of the bowel as well as in the mucosa and submucosa.

APPLICATION OF INTRACÆCAL INOCULATIONS.

It is evident that there is considerable opportunity for the use of more exact methods for the production of amœbic infection in animals. In our own experience, the use of intracæcal inoculation has afforded certain advantages over the usual methods. In the first place, we feel that it was in part responsible for the propagation of a strain of *histolytica* through a larger series of animals than has heretofore been obtained. It would seem to be a comparatively simple matter

to keep actively infected animals on hand for at least several months, a period sufficiently long for studying many of the ordinary problems of dysentery.

In the usual routine of the examination of patients, the diagnosis of amœbic dysentery must rest altogether upon the clinical conditions and the morphology of the entamœbæ. Animal inoculation has not been of any assistance in the diagnosis of individual cases since the inoculation of pathogenic amœbæ too often fails to infect the animals. In two instances of obscure diarrhœa which were studied the symptoms of the patient were so unusual and the amœbæ were so scarce and so atypical that there was no justification for the diagnosis of amœbic infection as the cause of the diarrhœa. Animal inoculation showed definitely that the cases were due to amœbic infection. Here we have then the infection of animals with material so poor in amœbæ and so atypical in morphology that a clinical diagnosis is not possible. This is quite the reverse of the conditions in which an abundance of virulent organisms from acute cases fails to infect animals. It may even be suggested that inoculation into a susceptible animal may prove to be a more delicate method of diagnosis than the microscopic examination of the stools. This would be especially helpful when patients are seen in the interim between attacks or in the determination of the pathogenesis of cysts found in carriers of *E. histolytica*.

The exact position of these atypical strains requires somewhat elaborate study in order to classify them. These amœbæ differ much more both in the clinical symptoms which they produce and in their morphology than many protozoa which are accepted as distinct species. However, rather than describe a new variety, it seems better to designate them simply as atypical strains of *E. histolytica* until their exact position can be determined. With a more certain method for the infection of animals, it is possible to study these atypical forms more extensively, and to test experimentally, whether some of the morphological characteristics of the amœbæ which are supposed to be constant, may not really be subject to variation.

Lastly, it is self-evident that there are many features in the routine which we have followed in these inoculations which require modification. In the first place, it is desirable to determine exactly the optimum site of injection into the intestine, both for cysts and for trophozoites, and the exact value of injury to the mucosa at the site of injection. As regards bacterial infection, we feel that many of the difficulties which we have had could be avoided. However, extremely virulent strains of bacteria can make their appearance without warning; streptococci may appear at any time which are sufficiently virulent upon injection per rectum to cause a fatal septicæmia during the incubation period of the amœbæ. It is certainly desirable to devise some precise method of avoiding the complications of bacterial infection.

SUMMARY.

I. The inoculation of kittens per rectum, or the feeding of dysenteric stools rich in amœbæ has been used for the production of dysentery with widely varying degrees of success, but, in general, about 50% of infections are obtained. It has

not been possible by either of these methods to propagate a strain of pathogenic amœbæ beyond a very limited number of passages.

II. Inoculation of eight strains of dysentery, some of which were distinctly atypical cases, directly into the cæcum, in ten kittens produced an infection in all instances. In some of the subinoculations considerable difficulty was experienced with bacterial septicæmia.

III. Some of the factors bearing upon the high rate of amœbic infection following intracæcal inoculations are as follows:

1. Absence of tendency to expulsion of injected material.
2. Optimum utilization of infective material and the avoidance in a large measure, of deleterious diluting agents.

3. Precision of the site of injection in the bowel.

IV. Definite evidence was obtained that the amœbæ are able to injure and penetrate the healthy mucosa. Unrestricted growth of bacteria in the intestine seems to be unfavorable to the entamœbæ. A marked suppression of bacterial growth in the amœbic lesion appears to be necessary for the best development of the pathogenic amœbæ.

V. Animal inoculation by intracæcal injection has been of assistance in the

1. Propagation of a strain of amœbæ through a series of animals for a period of several months;
2. Determination of the etiology of some obscure diarrhœas;
3. Study of the morphology of some atypical amœbæ of low virulence.

ANALYSIS OF A CASE OF PSYCHASTHENIA.*

By HENRI FLOURNOY, M. D.,

Interne, Henry Phipps Psychiatric Clinic.

The case which I wish to discuss is that of a man 28 years old, who suddenly developed the idea that he would have to kill his child. For five months this idea persisted without any change, then it disappeared and was replaced by the thought of killing himself. About two months after the development of this suicidal impulse the patient decided to come to the Henry Phipps Psychiatric Clinic for treatment.

A mental disorder of such a nature where one abnormal idea suddenly appears and remains in the mind of an apparently healthy individual is very similar to what occurs in cases of paranoia. The nature of such an idea, however, is different, as in the paranoiac it consists in a wrong interpretation of a limited part of the outside world—a systematic delusion not recognized as such. In the present case there was no delusion, but the patient referred to the ideas of killing his child or of killing himself as "harassed feelings" which he had to fight. He was conscious of his abnormal trend of thought, although he could not understand its mechanism. By analyzing his feelings and by trying to find out the why and wherefore of several incidents which had occurred before the onset of his obsession, when we found that he had once suspected his wife of infidelity and had sometimes doubted if the first child was really his, the idea of killing the child became much clearer in view of these facts which he had repressed.

In cases of this nature, it is advisable to take into consideration the slightest incidents preceding the onset of the disorder, and it is important to see clearly the inner conflict out of which the obsession might have sprung. By such a method of procedure our patients are put in the position of being able to understand the cause of their abnormal thoughts and to get rid of them. If they did not have such help, thoughts of an obsessive nature might cause more or less serious consequences, according to their nature and strength.

In 1846 Baillarger¹ reported the very striking case of a farmer, who, at the age of 17 years, developed the idea of killing his mother. He was unable to account to himself in any way for the onset of this idea. For 20 years he fought against it, and it was so strong that on two occasions he enlisted in the army so that he might be away from home. At the age of 37 this obsession gave way and was replaced by the idea of killing his sister-in-law. A few years later the patient consulted a physician, who gave him a certain amount of advice and bled him, but his frightful thought did not leave him. At the age of 43 he felt that he could not resist carrying out the act any longer, and to safeguard himself he begged his family and a physician to have himself locked up in an asylum.

From a diagnostic viewpoint we are dealing here with a type of obsession on account of which the patients feel, contrary to their conscious wish, a strong tendency to execute an act of the consequences of which they are afraid. Such a condition is closely akin to other obsessions characterized by doubts, impulses or phobias. Although disorders of this nature are usually described under the name of psychasthenia, yet they do not constitute a clean-cut disease, but should be considered as the results of previous and deeper difficulties. In each case an attempt should be made to understand the mechanism of the disorder by analyzing the concrete situations with which the patient had to cope.

S. H., a traveling man, 28 years old, was admitted to the Psychiatric Clinic in December, 1913. His father had died from chronic alcoholism, but otherwise the family history was negative.

Except for the ordinary diseases of childhood, the patient had always been in good health. He is stated to have been clever at school.

At home he was severely treated, especially by his father, who would not allow his children to have any recreation. He has, however, been a steady workman, having been employed by the same firm since his fourteenth year.

* Read at a meeting of the American Medico-Psychological Association, May 28, 1914.

¹ Annal. Med. Psych., 1846, 8, p. 10, quoted in *Traite de pathol. ment.*, p. 752.

He married at 20. His wife and two children, both girls, 3 years and 8 weeks, respectively, are all healthy.

The physical condition of the patient is good. Apart from a slight irritability, there is no apparent mental trouble. His memory, his power of retention of recent impressions, and calculation are normal. There is no history of alcoholism. The patient is of a cheerful disposition, and has always been strictly devoted to the Roman Catholic Church, in which he was brought up.

His only complaint was that six months previous to admission he suddenly developed the fear that he might kill his first baby. During the month just preceding admission this fear faded away and was followed and replaced by the idea of killing himself. The patient consulted his physician and his confessor, and both of them advised him to fight against such ideas, but as he could not succeed, he got the impression that this thought of harming himself was a punishment for his sins.

On admission (Dec., 1913) the patient said: "I want to get rid of these worrying and harassing feelings, which I have had since June 2, 1913." On that date the patient had been in a southern city on a sales trip, while his wife and child had remained at home.

One morning on getting up feeling as well as usual the obsession, the onset of which he describes as follows, suddenly came to him: "After my bath, I stretched my arms out, a morning stretch, then *like a flash* the thought came over me that I was going to harm in some way or to kill my baby. This thought frightened me terribly and I tried to get rid of it, but I could not do it. Then I went out to work with this thought with me. I fought this way for five days, until I decided to come home, and I have been fighting it ever since."

In reviewing the history of his life, the patient gave the following important facts:

As a child, he had lived in constant fear of his father, who, being quick-tempered and sometimes drunk, used to beat his children and his wife. The patient had not only had a deep affection for his mother, but a feeling of pity and sensitiveness, as he frequently saw her maltreated or threatened. When he was 17 years old he left home to escape his father's supervision and to earn his own living. He soon began to satisfy all his desires, and indulged in sexual relations in an excessive manner until he married at the age of 20 years.

His wife had become pregnant by him four months before marriage, when they were engaged, and an abortion was performed in order to avoid a scandal. This episode created a deep religious conflict in the patient, as the abortion for which he was responsible was a sin strictly forbidden by the Catholic Church. Although he was forgiven by his confessor, his feeling of responsibility became unbearable. The patient gave an account of the conflict which ensued in the following words:

"At the time I always was convinced of my fault, but I would like to think that it was not my fault, on account of my responsibility to God. I never doubted that I was the cause of the abortion, but, *from a spiritual standpoint*, I would have been glad to hear that I had not been guilty, that means, that I could have excused myself possibly if I had been in the position to doubt my wife." So the patient was already willing, before they were married, to cultivate unjustified suspicions towards her, and the thought that another man might have been the cause of the pregnancy, and consequently of the abortion of his fiancée, was in keeping with his wish to avoid the responsibility of his act. He knew that his wife had never had anything to do with any other man, but he brooded over this suspicion to relieve his conscience.

After the marriage they lived at his mother's home. The patient then began to suffer greatly over the difference in the social standing of his mother and sister and of his wife, the latter belonging to a higher class. As he was very affectionate and touchy concerning his mother and sister, he felt the superiority of his wife's education with uneasiness and resentment. The patient stated very

clearly that it would have given him some instinctive satisfaction if he had found that she was lower in some way. Here again the moral side was the only one where she might have been inferior, so that the patient's tendency to suspicion was increased after marriage, "always trying, he says, to find something wrong in her life, of which I could accuse and suspect her."

The only episode about which he thought he had ground to accuse her happened one and one-half years after marriage. One evening one of his friends came to his home to take him to the theater. As the patient was dressing his friend remained in the dining room in company with his wife. Suddenly the patient, who, from his own room, could scarcely hear their conversation, misunderstood a word and jumped at once to the conclusion that she had deceived him. "I just went up in the air. I was like a crazy man. I think the first thing I did was to tell this fellow that I couldn't go with him, I was sick. He left alone and then I started to fight with my wife. I remember that I accused her of everything under the sun, and that I pushed her violently down on the couch and accused her of having been untrue to me that afternoon with this fellow." His wife denied everything and all his further attempts to get any proof failed.

After he had worried one year about this matter without reaching any conclusion, he decided not to think any more about it and to banish it from his mind. Five years later, however, while in the hospital, he stated in a very frank manner that he had not allowed this idea of infidelity to come into his mind for several years. When advised to make this point clear, he answers: "I don't like to think of that," which is a good example of a voluntary repression, where the patient tried to keep away from his own mind the unclear and painful feeling of perhaps having been deceived.

It must be remembered that he himself, since marriage, in spite of his passionate nature and of the many temptations he had in his traveling profession, had always been true to his wife. In February, 1911, four years after the incident of suspicion, the first child was born, to the entire satisfaction of the patient and his wife. But when she was pregnant again in 1913 both were dissatisfied, because for financial reasons they did not want another child so soon. The question of an abortion arose again, but was declined at once, for the patient would not burden himself with this guilt a second time. Following this he became nervous and irritable, but accepted the idea of having a second child up until June 1, 1913, when a new incident brought back the old difficulty of the suspicion towards his wife, which for five years he had not thought about.

Towards the end of May, 1913, he had met a young girl on the trip already mentioned, whose company he enjoyed. On May 31, 1913, she told him that she had had relations with a friend of his, and following this he brooded and felt ashamed of his friend, who had been untrue to a faithful wife. He also experienced a feeling of jealousy, as he himself had had a strong liking for the girl, which, out of respect for his own wife and child, he had to master.

The next morning, June 2, the thought of killing the first child flashed into his mind. This obsession gradually disappeared, when at the end of October the second child was born, but only to be replaced by the fear that he would kill himself.

He describes the obsessive character of such fears, when he says: "The impression would come to me that I could not do such a thing, then instantly the thought would follow that no matter what I did to fight against these feelings, the inevitable result would be, that I would do it."

He fought several months, but never tried to find the reasons which could explain such thoughts. He did not think that they might have any connection with previous causes of worry, such as the suspicions he had had towards his wife; however, he cooperated in the review of the whole situation which revealed the above data.

At this point in the analysis the probable mechanism of the obsession was assumed to be as follows:

While ruminating over a possible intrigue with the girl the conflict between his instinctive impulse and his duty as husband and father was unusually strong, and the suspicion perhaps that he had once been deceived by his wife would have come into his mind, if he had not been in the habit of banishing it. He did not think of it. This old question was again repressed, but the situation was too hard to cope with, and the smaller and more recent difficulty of his married life, viz., the idea of soon having a second child, helped to determine the form of the obsession, that is, the frightful idea of killing his child, replaced later by the fear of killing himself.

The above explanation was given to the patient on the 4th of January, and on the 5th he felt relieved. The obsession to kill himself did not come any more, and when he thought of it there was no fear.

Six days later he again began to have a slight feeling of uneasiness concerning his first child, with fear of harming it. A deeper analysis of old memories and of his dreams showed still more definitely how this obsession was closely connected with his suspicions of his wife. The patient had doubted sometimes if this child was his, although he had never allowed this doubt to remain in his mind.

When compelled to reason out the situation, he finds that the only man whom he suspects his wife to have been with died at least one year before the child was born, and he says: "While not for one second I ever gave it a thought to question the birth of either one of my babies, I feel relieved to know that they are both mine, especially my first baby, because I have absolute proof."

In view of this revelation of the patient's latent doubts as to the paternity of the children, chiefly the first one, the probable mechanism of his obsession became somewhat clearer. His fear of harming the child disappeared again.

Discussing also why he had once accused his wife of having deceived him, he realized how blindly he had jumped to a conclusion; the more he thought of it the more he got convinced of her faithfulness, whereas the only suspicion could be the word which he misunderstood. "All these reasons tend almost to give me an absolute proof that I have been mistaken. I never tried before to

reason this whole thing out in any way. When the matter came to my mind, at first, I asked my wife over and over again, and she denied it always in the same frank manner; however, I was never convinced because I never reasoned it out myself. Later I banished this question when it came. I have not had an occasion to suspect her afterwards."

This statement shows what a strong tendency the patient had to suspect his wife. "Before meeting her, my impressions of women were that they were very weak, easily persuaded to do wrong, but I did not realize that men were just as weak. I had always been kept down at home, not allowed to have much company and thus got this impression of women from my father's treatment of my mother."

Such an explanation is only very superficial, but since it comes from the patient, it shows that he realizes how far back the roots for his suspicious state of mind are to be found in himself, more than in the behavior of his wife.

The patient left the Clinic February 14, 1914. He felt perfectly well until March 10, when a slight difficulty with his wife made him feel a little uneasy about his children. He got quickly over this trouble and felt well again.

The striking points in this case are:

(a) The sudden onset of an obsessive fear that he would kill his child, then that he would kill himself, against which the patient fought in vain for seven months.

(b) The disappearance of the obsession as soon as the patient saw that it could be connected with previous difficulties.

(c) The persistence of an uneasy feeling towards the children, without fear, arising at times when the patient is depressed or crossed.

The whole trouble is closely related to a suspicious state of mind, a fact which the patient had to realize. His prospect of avoiding a relapse of the obsessive fears depends greatly on the extent to which he will be able to assume a new mental attitude towards his wife.

FIBRINOLYSIS IN CHRONIC HEPATIC INSUFFICIENCY.*

By E. W. GOODPASTURE, M. D.,

Instructor in Pathology, Johns Hopkins University.

(From the Hunterian Laboratory of Experimental Medicine, Johns Hopkins Medical School.)

In the course of a study of the blood in hemorrhagic conditions a case of very advanced hepatic cirrhosis came under observation. The patient had been bleeding frequently and freely from the nose, mouth and rectum. Her condition was extreme and shortly she came to autopsy. Blood was drawn from the heart soon after death. It clotted firmly in normal time. Three and one-half hours later the clot had completely dissolved, leaving no trace of fibrin.

Following this we observed specimens of blood from many patients with various diseases to see if any clot would undergo a similar dissolution.† The study has included four cases of

atrophic hepatic cirrhosis, which have come to autopsy; and it is the interesting phenomenon of "fibrinolysis" in their blood which constitutes the subject of this paper.

The term "fibrinolysis" was first used by Dastre,¹ in 1893. He coined the word to designate the phenomenon of fibrin dissolution in serum. Whipped fibrin left in its own serum 18 hours lost on an average 8% in weight. Dastre called attention to this as a possible source of error in quantitative estimations of this proteid. He worked with the blood of dogs.

Despite this initial loss in weight of fibrin a clot from normal blood will not undergo complete dissolution for a very long time. It may be incubated at body temperature for days, or weeks even, without entirely liquefying, if kept sterile. In fact it is a matter of days, as a rule, before one can detect with the eye any change in the clot. This extremely slow autolysis

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of blood has been long observed. Under certain experimentally induced conditions, however, fibrinolysis may become very active. For instance, Jacoby,² in 1900, studying the relation of changes in liver and blood in phosphorus poisoning to autolysis, observed that blood from a severely poisoned dog was actively fibrinolytic. Blood drawn from this dog at the height of intoxication would not clot, owing to an absence of fibrinogen; but when normal blood was added to it the mixture clotted readily. After a while the clot was completely dissolved. Other observers have called attention to active fibrinolysis in the blood of phosphorus poisoned animals, but rather incidentally as Jacoby did.

In 1905 Nolf³ discovered fibrinolysis active in the blood of dogs which had received intravenous injections of proteoses. He observed the same condition likewise in animals after extirpation of the liver.

Years before Dastre called attention to fibrinolysis in serum, the fact that fibrin dissolves in dilute solutions of certain salts, like KNO_3 , NaCl , $[\text{NH}_4]_2\text{SO}_4$, Na_2SO_4 , was well known, and had given rise to much work and discussion.⁴ The outcome of these investigations was the proof that dissolution of fibrin under such conditions was not due to putrefaction, and the probability that it resulted from proteolytic activity of enmeshed leucocytes, rather than from a simple physical dissolution without chemical change—a view held by Hammarsten and others. Dastre himself believed the dissolution of fibrin due to a process of digestion, for he found proteoses and peptones were formed as a result of it. He imagined the salts acted like a proteolytic ferment. Rulot⁴ upheld the leucocytic theory of digestion, and showed that when the white corpuscles were eliminated very little digestion of fibrin took place.

The problem of an active fibrinolysis in serum is even more complex and difficult to explain satisfactorily. For here one has to deal with another factor, namely, the well-known antiproteolytic property of blood. Granting the dissolution of fibrin in serum to be due to enzyme activity, two main possibilities suggest themselves to explain it, viz., (a) great increase of proteolytic ferment overbalancing the normal antagonistic property of the blood, and (b) a diminution or absence of antiproteolytic substance, permitting the normal proteolytic ferment to act.

Morawitz,⁵ in 1906, studying post-mortem changes in human blood, noted the rather frequent occurrence of fibrinolysis of intravascular clots in bodies autopsied sometime after death. In one case the blood was completely fluid and no fibrinogen could be demonstrated as soon as ten hours after death. Morawitz states that fibrinogen can be destroyed, probably by fibrinolytic ferment, before any clotting occurs post mortem. Of his cases those that met a sudden death were more likely to exhibit post-mortem fibrinolysis.

Aside from the statement that blood in severe cases of leukemia may become proteolytic,⁵ I have found no reference to the ante-mortem occurrence of pathological fibrinolysis* in

human disease. Recently Saxl⁷ investigated the proteolytic power of normal and pathological human sera toward peptone. After two days, the shortest interval of digestion in his experiments, there was some proteolysis by the serum of each of the 26 cases studied, including a case of cirrhosis hepatis. The difference in amount of digestion was not striking.

In the following cases of cirrhosis fibrinolysis has been very rapid and clean cut:

CASE I.—Med. Hist. No. 31530. B. H., age 55, white female. Admitted to J. H. H. October 1, 1913. Complaint: pain in stomach, shortness of breath. F. H.: negative. Headaches for several years, short of breath for two years. Has had bloody stools for two years. Marked alcoholic history, usually 12 to 18 bottles of beer a day, since the age of 16.

P. I. began three months ago with enlargement of the abdomen. Skin yellow for four months. Occasional epistaxis. Vomiting of greenish material with no loss of blood. Day before admission patient began to be mentally dull. P. E.: scleræ have yellowish tinge. Heart dullness 14 cm. to the left; soft, blowing systolic murmur. Abdomen distended, numerous large veins over the lateral portions. Small area of tympany in the umbilical region. White blood cells 21,800. Hb. 70 per cent. Day of admission tapping was done; 6½ liters of turbid, yellow fluid removed, containing 2200 white blood cells per cu. m. Sp. Gr. 1012. Palpation after tapping, liver edge just felt; dullness to the costal margin; no masses; tenderness.

October 3d. Patient has been comatose since admission. Definite impairment of percussion note over the right base up to the 6th spine of the back. Breath sounds feeble. Numerous rales. Tendency to bleed rather freely from nose, gums and rectum.

Impression: Cirrhosis of liver, toxic stage; bronchopneumonia of right lower lobe. Urine: Sp. Gr. 1012, trace of albumin. No casts.

Anatomical Diagnosis.—Cirrhosis of liver; chronic fibrous tuberculosis (apex of left lung); acute tuberculous bronchopneumonia (apex of left lung); tuberculous peritonitis; chronic diffuse nephritis; hemorrhagic and diphtheritic gastritis; chronic splenic tumor; bronchopneumonia; bronchitis; tracheitis; jaundice; bilateral ovarian cyst; bilateral hydrosalpinx; ulcerative vaginitis; tuberculous bronchial lymphadenitis (caseation); chronic fibrous pancreatitis; chronic tuberculous perihepatitis and perisplenitis; accessory spleen.

Body is that of an obese white woman, 155 cm. long. The pupils are equal and not dilated. The conjunctivæ, mucous membranes and skin, especially of the face, show a marked icteric tint. There is a puncture wound from tapping in the midline below the umbilicus. The abdomen is rather full and slight fluctuation is made out. Lineæ atrophicæ are present on the abdomen. The right leg is 8 cm. shorter than the left. This shortening is in the thigh. The femur is bent and thickened. The bend occurs about the junction of the middle of the lower third. The right lower leg has a number of old cutaneous scars. On incising the body there is abundant panniculus. The abdominal cavity contains a considerable excess of yellow, slightly turbid fluid. The omentum is thickened and laden with fat, and is slightly rolled up over the transverse colon. The blood vessels of the mesentery and peritoneum are injected, and over all the peritoneal surfaces are thickly scattered, small, translucent, slightly elevated granules about ½-1½ mm. in diameter. Some of these have a yellowish center and practically all of them have a slight halo of injection around them. These granules are distributed everywhere but are perhaps more numerous in the flanks and pelvis and also in the more means by a pathological fibrinolysis. From our observations we have concluded that any blood whose clot dissolves completely in 12 hours at body temperature is pathological.

* Since the clot from any specimen of blood will in all probability undergo a certain amount of dissolution if left in its serum a sufficient length of time, it becomes necessary to define what one

exposed portions of the mesentery and intestinal coils, although this distribution is not very marked. The liver is small, the edge lying slightly above the costal margin, and it is very firm. The gall bladder is adherent to the colon and omentum, and there are numerous adhesions about the pelvis, where a large, rounded, cyst-like body projects upward above the pelvic brim on the right side. On opening the chest it is found that the diaphragm has been pushed upward, to a slight extent lessening the size of the thoracic cavity. The heart lies in a normal position. The pleural surfaces are smooth and glistening.

Liver weighs 1425 gm., measures $23 \times 14 \times 8\frac{1}{2}$ cm. It is of a very remarkable firmness, resembling hard rubber. The outer surface has a few small, opaque granules as described above. Aside from these it is very rough. The lobules are outlined by depressions. It is also mottled in color; the centers of the lobules appear to be yellow, while the remainder is of a darker tinge, while in some places there is grayish material resembling connective tissue. On section the lobules are readily seen. The liver tissue, however, seems to be compressed into a very small area. In every case it is bile stained. The portal zones are very thick and seem to be composed mostly of grayish, translucent looking tissue. Throughout them are many tiny blood vessels which in places give the portal zone a purplish appearance. In a few places are seen tiny, yellow, opaque dots, distributed without relation to the lobules.

Microscopically the liver shows well marked but not extreme annular cirrhosis. Central congestion and fatty change. Advanced repair. In connective tissue, well marked mononuclear infiltration and vascular congestion.

Blood Examination.—Blood was drawn from the heart one hour after death. It was hydræmic and had not yet begun to clot intravascularly. Five minutes after withdrawal it clotted firmly. A portion of blood was drawn into 1 per cent sodium oxalate to prevent clotting. This was centrifuged, and 20 cc. of the supernatant plasma used to determine the amount of fibrinogen. The plasma was bile stained and faintly alkaline to litmus. A part of this plasma was used for coagulation tests and tests for fibrinolysis.

The coagulation time was normal:

1 cc. plasma + 1 drop CaCl_2 (1%) = clot 6 minutes.

The original clot from the heart's blood and specimens of clotted oxalate plasma were placed in the thermostat at 37°C . In three and one-half hours they were fluid again. The clots had completely dissolved.

The plasma was capable of digesting dog's fibrin in small amounts, but was inhibited by dog's plasma in larger amounts.

1. .25 cc. human plasma + .75 cc. dog's plasma + Ca 2 drops = clot = no fibrinolysis 24 hours.

2. .5 cc. human plasma + .5 cc. dog's plasma + Ca 2 drops = clot = partial fibrinolysis 24 hours.

3. .75 cc. human plasma + .25 cc. dog's plasma + Ca 2 drops = clot = complete fibrinolysis 4 hours.

Inhibition of fibrinolysis by dog's serum.

1. .5 cc. human plasma + .5 cc. dog's serum + Ca 1 drop = clot = complete fibrinolysis 15 hours.

2. .5 cc. human plasma + .5 cc. normal salt solution + Ca 1 drop = clot = complete fibrinolysis 3 hours.

Tests made with oxalate plasma on three successive days showed a marked diminution in fibrinolytic activity. Whereas the clot digested in three and one-half hours on the first day, it digested in nine hours on the third day. After heating clotted oxalate plasma at 60°C . for 30 minutes no fibrinolysis took place within 12 hours.

Fibrinogen estimation yielded the low quantity of .183 gm. per 100 cc. blood plasma. This is about one-third the normal fibrinogen content of human plasma.

SUMMARY.—White woman, age 55, with ascites, leucocytes 21,880, jaundice and bleeding from nose, gums and rectum, came to autopsy. Liver showed typical atrophic cirrhosis.

Blood drawn from heart immediately after death clotted in normal time. The clot dissolved completely in $3\frac{1}{2}$ hours. Digestion of clot was inhibited by the addition of dog's serum to oxalate plasma. Heat at 60°C . for 30 minutes also inhibited digestion. Fibrinogen content of this plasma was .183 gm. per 100 cc.

CASE II.—Med. Hist. No. 31476. Autopsy No. 4024. G. T., age 47, white male. Admitted September 19. Complaint: swelling of abdomen and legs. Always in good health. Typhoid fever 15 years ago. Has had bleeding hemorrhoids for 15 years. Marked alcoholic history.

P. I. began four months ago with tenderness and swelling of abdomen, dyspnoea. Bleeding from hemorrhoids.

P. E.: On entrance icterus, collateral circulation noted. Impairment at both apices. Oedema of scrotum and legs.

Clinical Impression: Cirrhosis of liver with pulmonary tuberculosis. Blood count 10,000 white cells. Hemoglobin 62 per cent September 20. Coagulation time longer than normal. Examination of larynx (Dr. Crowe) showed reddening and granulation. Diagnosis: Tuberculosis probably. Wassermann negative.

October 3d. Abdominal tapping. October 5th. Rise in temperature to 104.8° and signs of pneumonia in right side. October 23d. Tetrachlorophthalein test gave 40 per cent output.

November 3d. Red blood cells, 1,952,000. White blood cells, 5600. Hb. 35 per cent.

Anatomical Diagnosis.—Diffuse cirrhosis of liver (atrophic type); chronic pancreatitis; passive congestion of abdominal viscera; chronic fibroid apical tuberculosis; chronic laryngeal tuberculosis; general anasarca; emaciation; bronchopneumonia (organizing); congestion and oedema of lungs; acute aortic endocarditis; acute splenic tumor; disseminated ecchymoses; intramuscular hemorrhage (puncture wound); bilateral inguinal hernia; blood abnormality—fibrinolytic ferment and low fibrinogen content; chronic gastritis; chronic ulcerative laryngitis (tuberculous).

Body is that of a large framed, somewhat emaciated white male, 179 cm. long. Rigor mortis is present. Icterus is evident over the neck and chest. The right arm and lower extremities show notable boggy oedema, and the subcutaneous tissues pit deeply on pressure. The scrotum is very oedematous and on incision is found to contain two large hernial sacs, the left being larger, its orifice admitting three fingers with ease. The short loop of the sigmoid is adherent by pretty tough adhesions to the neck of this left inguinal hernia. The testicles on section appear normal. On section through the abdominal wall one opens into a cavity containing bloody fluid. This is just below the puncture wounds (abdominal tapping). The extravasated blood had been completely digested, soft and fluid. It had burrowed laterally in the sheaths of the recti and in the properitoneal fascia, extending down in the pelvis in the neighborhood of the bladder and representing in all perhaps 100 cc. of blood. The abdominal cavity contains about $\frac{1}{2}$ liter of clear, lemon yellow fluid. The peritoneal surfaces are smooth, but show milky patches of thickening, more especially about the root of the mesentery. The omentum and mesentery are rich in canary colored fat. There are a few adhesions about the spleen, but the liver is free. The thorax is barrel shaped. On opening the pleural cavities they contain an excess of clear, lemon yellow fluid. There are dense adhesions over both apices. The pericardial sac contains an excess of fluid, slightly blood tinged, due to the aspiration of blood shortly after death.

Liver weighs 1480 gm. It presents the typical picture of Lannec cirrhosis. The capsule is thickened and rather milky. The surface is coarsely granular, showing warty areas sticking above the surface. Collateral circulation in the suspensory ligament is very conspicuous. The gall bladder is dilated, thin walled, but the bile passages are normal. On section parts of the organ show very

extensive scarring, whereas other portions show a more diffuse and not so extensive involvement. There are nodules and lumps of liver parenchyma of all sizes between the scars. These nodules may be gray or pigmented yellowish-brown. There are bright red areas apparently associated with hemorrhage and perhaps necrosis, in some of the liver cells. The architecture is greatly obliterated. The left lobe is thin, flattened and elongated, but in general presents the same changes found in the right lobe. The organ is very firm and hard. The mucosa of the gall bladder is normal.

Microscopic Sections.—Liver shows the usual picture of diffuse cirrhosis in which dense connective tissue is not very conspicuous. The mononuclear cell reaction is quite pronounced. Icterus is present in some lobules. A good deal of liver epithelium is well preserved and only slightly distorted. Some liver cells show hypertrophy. The new formed bile duct reaction is not striking. There are some focal necrosis. The necrotic cells are often bile stained.

Blood Examination.—Blood from this case was first examined October 21, 1913, one month before death. It was quite hydræmic. At this time the fibrinogen was .3435 gm. per 100 cc., just below the limit of normal. Blood drawn from an arm vein clotted firmly in normal time. Clots from whole blood and from oxalate plasma were placed in the thermostat at 37° C., and at the end of 16 hours were completely fluid. The specimens were not examined at intermediate intervals, consequently the exact time of complete dissolution is not known. In this case fibrinolysis was inhibited by cat's plasma in all dilutions used up to equal parts.

1. .5 cc. cat's plasma + .1 cc. human plasma + Ca 1 drop = clot = no fibrinolysis 24 hours.
2. .5 cc. cat's plasma + .5 cc. human plasma + Ca 1 drop = clot = no fibrinolysis 24 hours.

Oxalate plasma kept on ice 48 hours, then clotted with calcium and incubated, showed only slight dissolution after 24 hours. There was also a definite diminution in fibrinolytic activity in plasma two or three days old, as in the previous case. Phenol-tetrachlorophthalein excretion in the feces at this time was normal, 30 per cent. Blood lipase was also normal.

One month after the above tests were made this patient came to autopsy. Blood was drawn from the heart within one hour after death. It was very watery, the cellular elements constituting only one-tenth or less of the total volume. The blood clotted five minutes after aspiration from the heart. The clot was jelly-like but firm enough to permit inversion of the flask without breaking. The fibrinogen had fallen to .0975 gm. per 100 cc.

Clots from whole blood and from oxalate plasma coagulated with calcium and with thrombin, dissolved completely within three and one-half hours at 37° C.

The following tests were made with fibrinolytic serum plus normal human plasma. The human plasma was obtained by receiving blood into iced paraffined tubes, centrifuging and pipetting off the supernatant fluid.

1. .25 cc. serum + .75 cc. normal plasma = clot = no fibrinolysis 24 hours.
2. .5 cc. serum + .5 cc. normal plasma = clot = no fibrinolysis 24 hours.
3. .75 cc. serum + .25 cc. normal plasma = clot = no fibrinolysis 24 hours.

These clots showed no fibrinolysis after incubating for three days, illustrating the inhibiting effect of normal blood.

No digestion of egg albumin was observed in Mett's tubes incubated in this fibrinolytic serum 10 hours at 37° C.

As in the previous cases fibrinolytic activity diminished greatly in plasma kept three or four days. The plasma used in the following experiment was three days old.

- 1 cc. plasma + Ca 2 drops = clot = partial dissolution 8 hours; complete 24 hours.

On the first day the clot dissolved in three and one-half hours.

SUMMARY.—White man, age 47, with ascites, jaundice, loss in weight, expectoration of blood, active bleeding piles, and leucocytes 5200, came to autopsy. The liver exhibited atrophic cirrhosis. One month before death blood drawn from an arm vein clotted in normal time. The clot dissolved completely in 16 hours, perhaps sooner. The fibrinogen content of the blood plasma was .3435 gm. per 100 cc. Serum lipase was normal. Phenoltetrachlorophthalein output in feces was normal, *i. e.*, 30%.

Blood drawn from the heart immediately after death clotted in normal time. The clot dissolved completely within 3½ hours at 37° C. Oxalate plasma clotted with normal thrombin dissolved its clot in the same time. Digestion of the clot was inhibited by normal human serum. Mett's tubes incubated 10 hours at 37° C. in fibrinolytic serum showed no sensible digestion. After three days clots formed by adding Ca to oxalate plasma, digested in 8 hours. Fibrinogen content of this plasma was .0975 gm. per 100 cc.

CASE III.—J. H., colored male, age 50. Admitted to Bay View October 8, 1913. P. I. began two weeks before admission with pain in left side, and swelling of both legs. Bleeding piles four years ago. P. E.: Ascites. Distention of abdominal veins. Occult blood in stools. W. B. C. 6000. Hb. 65 per cent. Died January 18, 1914.

Anatomical Diagnosis.—Atrophic cirrhosis of liver. The liver was lobulated in gross and under microscope showed diffuse increase in connective tissue, and hypertrophic nodules of liver cells.

Blood Examination.—On December 13, 1913, this patient was bled. On the following morning, 13 hours after its formation, the clot was completely dissolved. Tests were then made with oxalate plasma. Clots formed normally on the addition of calcium and completely dissolved when incubated four hours at 37° C. At the same time these tests were made specimens of clotted plasma were heated on a water bath at 60° C. for 30 minutes, then incubated. They showed no fibrinolysis. Heat completely destroyed their activity.

On the same date these experiments were made, a phenoltetrachlorophthalein test was done. The excretion was very low, being only 5 per cent. Lipase was also low.

The patient was bled again on December 16, and the above tests repeated with similar results. Fibrinolysis was complete in four hours. It was destroyed by heat at 65° C. for 30 minutes, and by adding to the plasma an equal part of normal human serum.

The fibrinogen content of this plasma was .120 gm. per 100 cc. One month later the patient came to autopsy. Unfortunately the blood was not examined at this time.

SUMMARY.—Colored male, aged 50, with ascites, occult blood in the stools, and leucocytes 6000, came to autopsy. The liver showed advanced atrophic cirrhosis. One month before death blood drawn from an arm vein clotted in normal time. The clot dissolved completely in 4 hours at 37° C. Heat at 60° C. for 30 minutes inhibited this activity. Fibrinogen content of this plasma was .120 gm. per 100 cc. The excretion of phenoltetrachlorophthalein was very low, *i. e.*, 5%. Lipase was low.

CASE IV.—W. J. K., white male, age 40. Admitted to J. H. H. November 21, 1913.

P. I. began one and one-half years ago with swelling of feet and ankles; later swelling of abdomen. In May, 1913, he vomited a large amount of dark blood. Stools contained much blood. Six days before admission patient vomited one pint of dark blood and

had bloody stools. Increasing œdema, ascites and dyspnœa. Considerable epistaxis for past year. Bleeds easily from small wounds.

P. E.: Poorly nourished; marked anemia, sallow. Scleræ slightly jaundiced. Ascites. Oedema of feet and ankles. Positive Wassermann. Improved under antisyphilitic treatment. February 20, 1914, surgical operation. Omentoplasty. Recovered from operation satisfactorily. Gradually became worse. Died May 14, 1914.

Anatomical Diagnosis.—Atrophic cirrhosis of liver; portal stasis; ascites; dilated collateral circulation; organizing thrombosis of portal vein and its radicles; chronic interstitial hyperplasia of spleen; chronic interlobular pancreatitis; pancreatic necroses; hemorrhages into the islands of Langerhans; chronic interstitial nephritis; jaundice; decreased fibrinogen; fibrinolytic ferment in blood; chronic fibrous pleuritis (right); bilateral atelectasis (lower lobes); chronic local peritonitis, perihepatitis and perisplenitis.

Body is that of a white man, greatly emaciated and extremely jaundiced. There is a scar of an old surgical incision over the right rectus extending longitudinally. The abdomen is distended and the lower border of the ribs protrudes on each side. There are no superficial abnormalities noted, except dilatation of the superficial veins over the abdomen and chest wall. There is no distinct caput medusæ but the superficial vessels generally over the abdomen and chest are enlarged. On section the subcutaneous fat is almost entirely wanting. The skin adheres pretty firmly to the bony structures. On opening the peritoneal cavity a great amount of orange colored fluid is present. The omentum is folded back and adheres to the anterior abdominal wall and the anterior portion of the liver. The liver cannot be seen. Its normal site is occupied by ascitic fluid. On passing the hand back over into this region the liver can be felt deep down as a small nodular mass which feels as if it were floating in fluid. The entire organ can almost be encompassed by the palm of the hand. The spleen is very large indeed. The surface of the small bowel is everywhere smooth, but there are many irregularly linear thickenings of the serous surface, and the wall of the gut is œdematous and thick. The vessels of the mesentery about the colon and of the omentum are greatly dilated. The omentum is adherent to the anterior surface of the liver in a few places, and the vessels are dilated. They are quite small and quite incapable of carrying on much circulation. On opening the chest wall the pleural cavity and pericardial cavity are found to contain a normal amount of fluid. The right lung is adherent to the chest wall above and to the diaphragm below by fibrous adhesions.

Liver is unusually small, presenting a uniform, advanced, atrophic cirrhosis. It weighs 810 gm. It is extremely hard and its surface is typically hobnailed—composed of nodules measuring up to 4-5 mm. in diameter, which are greenish-yellow in color, surrounded by depressed connective tissue in which are dilated venules. Just above the gall bladder is a large, depressed scar which measures 4 x 5 cm. in diameter. Beneath this scar about 1 cm. below the surface is found the main branch of the portal vein almost completely thrombosed, and as the scarring above this follows the course of the vein, it seems quite probable that thrombosis of the vein had to do with the atrophic scarring. In the scar there are no dense connective tissue bands, but small ducts, and the vessels can be seen indicating a simple atrophic scar rather than one formed with proliferative connective tissue. On section the liver has lost its normal architecture, and the cut surface is composed of greenish, orange areas of hypertrophic parenchyma. These areas measure up to 5 mm. in diameter and correspond to the nodules of the surface and are surrounded by depressed scar tissue.

Microscopically the liver is found to be composed of a net work of connective tissue bands surrounding islands of large and small

liver cells. Mononuclear infiltration and bile duct proliferation are quite evident.

Blood Examination.—On November 25, 1913, liver function tests were done on this patient. Except for a rather low fibrinogen, .222 gm. per 100 cc., there was no abnormality. Active fibrinolysis was present. Blood was drawn on November 25. It clotted normally and was kept on ice over night. Next morning the clot showed little change. It was placed in the thermostat and became completely fluid in five and one-half hours.

This patient came to autopsy May 14, 1914. Blood aspirated from the heart immediately after death showed marked anemia. Clotting time was normal. Complete fibrinolysis occurred on incubating the clot for five hours at 37° C. The fibrinogen content had fallen to approximately .150 gm. per 100 cc.

SUMMARY.—White male, age 40, with ascites, œdema, jaundice, tendency to bleed, anemia and positive Wassermann, eventually came to autopsy. The liver was in a state of extreme atrophic cirrhosis. Six months before death his blood clot dissolved on incubating it 5½ hours at 37° C. Fibrinogen content of the blood at this time was .222 gm. per 100 cc. Serum lipase was normal. Phenoltetrachlorophthalein excretion was normal.

Blood drawn from heart immediately after death clotted in normal time. Its clot dissolved completely in 5 hours at 37° C. Fibrinogen content of this plasma was .150 gm. per 100 cc.

SUMMARY OF CASES.*

Case.	Date.	Fibrinogen gm. per 100 cc. blood.	Fibrinolysis complete.	Phenoltetrachlorophthalein	Blood lipase
Normal..450	Days	30-40%	0.25
Case I...	10/ 6/13	.183	3½ hrs.
Case II..	10/21/13	.350	16 hrs.	30%	0.28
Case II..	11/19/13	.0975	3½ hrs.
Case III..	12/13/13	.120	4 hrs.	5%	0.19
Case IV..	11/25/13	.222	5½ hrs.	30%	0.28
Case IV..	5/14/14	.150	5 hrs.

* Phthalein and lipase figures are from tests made by Rowntree, Marshall and Chesney.

Specimens of blood from fifty cases on the wards with various diseases have been incubated at 37° C. for several days without the clot completely digesting. Even when no aseptic precautions are taken dissolution is exceedingly slow. No case of atrophic cirrhosis has come under our observation during this study that has not shown active fibrinolysis of its blood clot.

DISCUSSION.

Herein are reported four cases of atrophic hepatic cirrhosis, the diagnoses of which have been confirmed by autopsy. In each the blood has exhibited the phenomenon of active fibrinolysis, to the extent that it dissolved its own clot completely within a few hours at body temperature. In three of the cases this property of the blood has been demonstrated sometime before death.

As to the nature of this process there can be little doubt that fibrinolysis is due to enzyme activity. All the above tests point to this. The activity is very pronounced at body temperature; it is greatly injured by heat at 60° C. and destroyed

at 65° C.; it is inhibited by normal serum. After standing two or three days a plasma gradually loses most of its activity, so that dissolution of its clot proceeds very slowly.

The clots are to all appearances normal. The thrombin factor does not seem to be at fault; for oxalate plasma clotted with normal thrombin digests its fibrin quite as rapidly as when coagulated with calcium.

These facts not only support the theory that fibrinolysis is the result of enzyme activity, but are positively opposed to the view of simple fibrin dissolution. Especially so is the fact that plasma gradually loses its power to dissolve the clot. There is nothing reasonable to support the latter hypothesis.

Whether the ferment is specific for fibrin is not evident. Certainly fibrin is attacked with much greater rapidity than egg albumin or fibrinogen. Mett's tubes showed no sensible digestion after incubating in fibrinolytic serum 10 hours at 37° C. Fibrinogen does not appear to be diminished in amount in plasma incubated 24 hours. It would be a pleasing theory to attribute to activity of the fibrinolytic ferment the low fibrinogen content encountered in these cases. Evidence, however, does not support this, and we have an adequate explanation of the low fibrinogen in the severe injury to the liver; for upon this organ fibrinogen equilibrium of the blood is principally dependent.⁸

We have no evidence of an absolute increase in the quantity of proteolytic enzyme in the blood of these cases. The existence of proteolytic enzymes in the blood stream, not derived from formed elements of blood, is not proven. It is known, however, that leucocytes contain such enzymes, capable of acting upon fibrin. Of the cases studied here only one showed an increase in leucocytes; the others were below normal in this respect. The proteolytic enzymes emanating from this source were presumably, therefore, not increased. There was no increase in serum lipase. The inhibition of fibrinolysis by the addition of small quantities of normal serum is against the presence of a large excess of enzyme.

With the meagre facts at hand it seems more reasonable to regard fibrinolysis as the activity of normal proteolytic ferments of the blood, operating by virtue of a diminution or absence of normal antiproteolytic substances. It would be useless to speculate upon this without further data, which we hope to gather from more extensive chemical studies of these bloods.

The cases herein studied have exhibited clinically the usual signs of advanced hepatic cirrhosis. They have all manifested a tendency toward hemorrhage; and their deaths have been such as might be in great part ascribed to what is recognized as hepatic insufficiency. Fibrinolysis has thus been associated with, (a) chronic liver injury severely impairing hepatic function, and (b) with a hemorrhagic tendency.

Its association with liver injury reminds us of the instances in which fibrinolysis has been observed under experimental conditions impairing liver function. It appeared in Jacoby's phosphorus poisoned dog. As is well known liver injury is extreme in fatal phosphorus poisoning. Nolf later observed the same phenomenon after extirpation of the liver of dogs.

We have not been able thus far to demonstrate active fibrinolysis experimentally in animals acutely poisoned with phosphorus and chloroform. A few human cases of acute liver injury with necroses have come to our observation. None has shown active fibrinolysis in the blood. Again livers severely injured by advanced chronic passive congestion, but which are apparently compensating, have not been accompanied by fibrinolysis. Its presence, then, has been associated in these cases only with a stage in chronic liver disease when the organ is severely impaired functionally.

Recently three tests for liver function have been proposed and employed by Whipple⁹ and by Rowntree,¹⁰ namely, estimation of blood fibrinogen and serum lipase, and the excretion of phenoltetrachlorophthalein in the feces. In acute liver injuries under experimental conditions these methods indicate pretty accurately the degree of the liver lesion. In chronic liver disease, cirrhosis of the liver, for example, only the fibrinogen estimation seems to offer any hope as a diagnostic and prognostic procedure. In grave hepatic injury resulting from an acute or chronic process the fibrinogen content of the blood drops, sometimes to very low amounts.

In the above cases the tetrachlorophthalein excretion was diminished in only one instance; the lipase was of no diagnostic value in any; and the fibrinogen content was low in all. In Case II the fibrinogen was only slightly diminished; the other tests were normal, while the fibrinolytic property of the blood was quite active, a month before death. This makes us hopeful that the presence of a ferment in the blood capable of completely digesting its clot may be of considerable diagnostic and prognostic value in chronic hepatic insufficiency. In four cases of cardiac decompensation with ascites we have examined, where there might have been a question of differential diagnosis from cirrhosis, the fibrinolytic ferment has not been active. Likewise it has been inactive in two cases of tuberculous peritonitis with ascites.

The association of fibrinolysis with a marked tendency toward hemorrhage is also of considerable clinical interest. In Case II there is little doubt that digestion of clots *in vivo* was an important factor in his bleeding. At autopsy was found between the peritoneum and abdominal wall beneath a paracentesis puncture, a hematoma as large as a hen's egg. On opening it dark fluid blood escaped. Evidently what clots formed had digested, permitting a continuous ooze. A low fibrinogen content obviously also predisposes to bleeding, by forming inefficient clots. Under experimental conditions, however, the fibrinogen must drop exceedingly low, *i. e.*, about 50 mm. per 100 cc., before one may confidently refer bleeding to this factor.

SUMMARY.

1. Specimens of blood from four cases of atrophic hepatic cirrhosis have possessed the property of completely digesting their clot within a few hours, at body temperature.
2. Normal blood will not digest its clot for days or weeks.
3. Dissolution of clot in the blood of cirrhosis cases is due to an enzyme. Its activity is destroyed by heat; inhibited by normal serum; and diminished in old plasma.

4. Fibrinogen content of the blood of each case has been below normal. Hydræmia was a constant feature. One case exhibited a low phenoltetrachlorophthalein output.

5. Digestion of clots in vivo explains in part the hemorrhagic tendency present in these patients.

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THE HIGH INCISION IN CÆSAREAN SECTION.

By W. L. THOMPSON, M. D., New York.

The high operation in Cæsarean section¹ possesses so many advantages over the procedure commonly in use in this country that it deserves a more wide-spread publicity, and a more general adoption than it has hitherto received.

The increasing frequency with which Cæsarean section is employed to overcome dystocia, replacing to a large extent the manoeuvres at the pelvic outlet, demands a more scientific procedure than the time-honored operation with its long, mutilating incision and undue exposure and manipulation of uterus and intestines.

The simplicity of this operation and the minimum handling of the viscera involved, commend it not only to the specialist, but to the practitioner who finds himself confronted with an obstetrical emergency. I have not hesitated to perform this operation in the tenement, assisted only by students, and have never seen any untoward effects from its performance.

The photographs accompanying this article reveal at a glance the superior cosmetic effect of the short incision, and (Figs. 1 and 3) the absence of the unsightly needle holes when subcutaneous suturing is employed.

Case 49 (Fig. 2) shows a cicatrix of 2½ inches. The operation was done at short notice, in a tenement house where all modern conveniences were lacking. The circumstances surrounding this particular case illustrate the abundant opportunities for clinical teaching afforded by a Cæsarean operation. The patient, an elderly primipara, had been in labor for twenty-four hours, with rigid, incompletely dilated cervix, and uterine inertia. I decided to perform Cæsarean section rather than forcibly to dilate the cervix and apply forceps, an operation attended with greater morbidity (when performed in the tenement under adverse conditions) than is celiotomy. I selected, as assistants, six students from the two upper classes, and for an hour rehearsed with them every procedure in the preparation for and performance of the operation. Then to each student I assigned a definite rôle and again coached him individually in his particular duties. A set of sterile dressings for laparotomy was obtained from a surgical supply house and a woman student, who had been a trained nurse, attended to the preparation of the patient and room.

¹ First described by Dr. A. B. Davis, New York City, in the Bulletin of the Society of the Lying-in Hospital of New York City, December, 1905.

During the operation, a senior student gave the anæsthetic, my assistant being a senior, while the two junior assistants, the nurse, and the man who handled the baby were from the third-year class. Although the assistants were preceptibly nervous at this, their first abdominal section, yet, by proceeding slowly with a little encouragement and coaching to each man and constant supervision of their technique, the operation proceeded uninterruptedly, with the delivery of a healthy baby and the mother in good condition. Convalescence was uninterrupted and the patient on her feet in 14 days.

TECHNIQUE.

Preparation.—One-half hour before the operation, the patient is given a hypodermic injection of "Ergot Aseptic," to insure proper tonicity of the uterus.

Besides the operator and the anæsthetist, three assistants are necessary: a first assistant, one to handle instruments and dressings, and a third to take charge of the baby.

The patient should be in the dorsal position, under full surgical anæsthesia with ether or chloroform.

The abdomen is prepared in the usual manner for celiotomy (especial attention being paid to the epigastric region), covered with a laparotomy sheet, and the site of the incision covered by sterile towels pinned together so as to expose the smallest possible area of skin.

Cutaneous Incision.—The skin and underlying tissues are opened by an incision 12 cm. in length (the width of the clenched fist), ending at the umbilicus. The peritoneal cavity is entered in the usual manner, the fundus uteri lying directly under the wound. The uterus is usually twisted on its long axis (dextro-rotation as a rule), and it will occasionally be found advantageous to manually readjust it.

Abdominal Toilet.—The intestines are carefully walled off with three or four Miculicz pads wrung out of hot normal saline. This is an exceedingly important point, as it effectually prevents exposure and handling, and minimizes the danger of contact of the intestines with the possibly infected amniotic fluid. The first assistant now places his hands on either side of the abdomen, well back toward the flanks, to steady the uterus against the anterior abdominal wall; this manoeuvre should be continued during the emptying of the uterus and until the deep sutures are tied.



FIG. 1, CASE No. 32.



FIG. 3, CASE No. 60.



FIG. 2, CASE No. 49.



FIG. 4, CASE No. 82.

Figs. 1-4 illustrate (a) the *location* of the incision above the umbilicus; (b) its *minimal size* 12 cm. (less than 5 inches) at the time of operation, which at the end of the puerperium has contracted to 6.5 cm. (2½ inches), as in Fig. 2, Case No. 49; and (c) absence of the unsightly needle holes when subcutaneous suturing is employed.

Uterine Incision.—A median incision is now made in the uterus well up toward the fundus, and slightly longer than the abdominal opening. The incision should be made by successive strokes of the knife to avoid premature opening of the amniotic sac. As the amniotic sac bulges into the wound, the incision is best completed by scissors.

Amniotic Sac and Membranes.—The amniotic sac is not opened immediately unless the placenta lies directly under the incision, when it is cut or torn through rather than peeled away, and the uterus rapidly emptied. If the membranes alone present, the hand is swept rapidly between sac and uterus to break up any possible adhesions which might cause dangerous delay at a critical moment. The sac is punctured with knife or scissors and an adequate opening completed with the fingers.

Extraction of Child.—As the majority of presentations are cephalic, delivery of the child amounts to a breech extraction, with the head delivered by Mauriceau's manoeuvre. Should the presentation be breech, internal podalic version is performed as in a delivery *per vias naturales*. The second assistant now clamps the cord in two places, the operator cuts between them, and hands the child to the third assistant who at once removes it from the operating room to establish respiration, thus allowing the operator to give his undivided attention to the patient.

Supporting Uterus.—After it has been emptied, the uterus immediately begins to contract, and tends to slip down in the abdomen. To counteract this tendency, the pressure of the assistant's hands on the sides of the abdomen is supplemented by two double tenacula applied one to either edge of the uterine wound at its upper angle, or by hooking the fore-finger into the upper angle.

Delivery of Secundines.—Membranes, placenta and clots are now removed *en masse*, by sweeping the hand over the entire inner surface of the uterus.

Suture of Uterus.—To close the uterine wound, deep interrupted sutures of heavy chromicized gut are best. These should be inserted 1 cm. from the edge of the wound, down to, but not through, the decidua, passed through the opposite side, emerging at a point corresponding to the point of insertion. Beginning at the lower angle, each suture is tied as placed, and tied tightly, more tension being made than in suturing an ordinary wound, to allow for contraction and retraction of the uterine muscle. If this is not done, the first sutures will be found loose and unserviceable by the time the later ones are tied. Often by the time two of these deep sutures have been placed and tied, they will have acted as sufficient stimulus to cause safe contraction of the uterus and check dangerous hemorrhage, while the remaining three or four sutures usually stop all bleeding.

Hemorrhage from Uterine Wound.—Occasionally, hemorrhage from the cut uterus is alarming; muscular tone seems wanting, the whole organ a flaccid, empty sac, with blood pouring from every conceivable surface. An extremely hot wet towel applied directly to the wound, or a dry sterile towel packed hurriedly into the uterine cavity, will often hold the

bleeding in check until the deep sutures have been placed; and on these sutures ultimate reliance must be placed to stop the hemorrhage, so that too much time should not be wasted in temporizing with other measures. When the blood is seen to come directly from the uterine sinuses, an attempt should be made to catch these with hemostatic forceps. If packing the uterine cavity has been resorted to, the packing should be gradually withdrawn as soon as the deep sutures are in place, and then these rapidly tied. Oftentimes this operation is performed with less loss of blood than in an ordinary labor, and without the use of an artery clamp, ligature, hot towel or other hemostatic agent from start to finish.

Superficial Uterine Sutures.—The deep sutures having been placed and tied, apposition of the uterine wound is completed by using enough interrupted sutures of fine chromicized catgut, superficially placed, to accomplish this. A running suture of fine catgut draws the peritoneum over the wound, burying the deep sutures, and minimizing the danger of adhesions between the uterine and abdominal wounds.

Closure of Abdominal Wound.—The uterine wound having been sutured, the exposed surface of the uterus is wiped clean with moist gauze pads and the abdominal packs removed. The latter will be found to have absorbed most of the blood and amniotic fluid. No attempt is made to irrigate the abdominal cavity.

While the abdominal wound is protected by a sterile towel, the surrounding skin is washed and wiped clean, the soiled towels removed, and a fresh toilet made with dry sterile dressings. In closing the wound, three sets of sutures are employed: continuous catgut for peritoneum and another for fascia, while the skin is best closed by a continuous subcutaneous suture of silver wire.

Dressing Abdominal Wound.—Sterile gauze pads are applied to the wound, and held in place by broad strips of adhesive. The vulva is covered by a suitable pad, and a T-binder applied.

POST-OPERATIVE TREATMENT.

As soon as recovery from the anæsthetic is complete, the head of the bed is raised enough to give a decided incline in order to favor drainage, and particularly to cause the uterus to sink downward toward the pelvis and away from the abdominal wound, to further minimize the danger of adhesions.

The silver wire suture may with safety be removed on the seventh to the ninth day; by grasping its free ends with hemostatic forceps and working the wire back and forth in its sinus a few times, its ease of removal is enhanced; one end is then cut off close to the skin and the remainder of the wire removed with a single quick pull.

Convalescence is as rapid and uninterrupted after this operation as the puerperium following a normal delivery. My patients have all been allowed to sit up on the tenth day, have walked on the twelfth, and have been going up and down stairs on the fourteenth with no untoward effects either upon their general well-being or the progress of involution.

There is no reason why as much deliberation should not be

exercised in the performance of this as in any other intra-abdominal procedure. At no time in the course of the operation is there need for haste, with the occasional exception of placing and tying the deep uterine sutures.

SUMMARY.

The salient features of this operation, which should give it first place among the procedures for Cæsarean section, may be briefly reviewed.

1. *Skin Incision*.—(a) Its *location*, high in the abdomen, above the umbilicus, renders it less subject to pressure than in the more convex and dependent portion; it receives better re-enforcement from the recti muscles whose edges are nearer together at this point in the parous woman, and whose support is greater as the upper attachments of these muscles are approached. Its location, furthermore, precludes all possibility of adhesion between it and the rapidly contracting and retracting uterus, whose cut surface, by the time the uterus is emptied, is far removed from the abdominal incision.

(b) Its *length*, only 12 cm. (less than 5 inches), see Fig. 4, in contrast with the usual incision of twice this length, leaves

an exceedingly short cicatrix which is rendered almost inappreciable by the practice of subcutaneous suturing, as is well illustrated by the accompanying photographs.

2. *Packing off the intestines* not only keeps them out of the way during operation, but in the event of repeated vaginal examinations under uncertain aseptic precautions, prevents the possibly infected liquor amnii from inoculating the abdominal contents.

3. *Leaving the uterus in situ* has more to recommend it than is at first apparent. It is an accepted fact that sudden reduction of tension in a body-cavity tends to induce shock (from acute cerebral anemia); such an accident is scarcely possible with the uterus in situ. The common practice of delivery of the uterus and manipulation of the intestines carries with it the constant danger of infection of these structures.

4. *Uterine Incision*.—The location of the incision in the thick, muscular fundus minimizes the danger of rupture in subsequent labors, whereas the long incision in common use extends into or encroaches upon the attenuated lower uterine segment and further increases its vulnerability.

NITROGEN METABOLISM BEFORE AND AFTER SPLENECTOMY IN A CASE OF PERNICIOUS ANÆMIA.

By GEORGE R. MINOT, M. D.,

Assistant Resident Physician, The Johns Hopkins Hospital.

(From the Chemical Division of the Medical Clinic.)

Von Noorden¹ in 1894 was the first to study accurately the metabolism in pernicious anemia. He was unable to show that protein decomposition was increased as a consequence of the anemia, though he states that earlier observers believed this to be the case. He has found in some cases a retention of nitrogen, and Von Stejskal and Eben,² Strauss² and Bloch² have also found the same; it is, perhaps, due to a previous underfeeding, or associated with periods of blood regeneration, as suggested by Mohr.³ Yet, with a rapid destruction of red blood corpuscles, there may be increased protein destruction.

Rosenquist⁴ found in cases of pernicious anemia that periods during which nitrogen excretion was increased alternated with those in which a retention occurred, but believed there tended to be a pathological decomposition of protein. Von Noorden¹ and Umber⁵ have suggested that Rosenquist's methods may have been at fault in the way he calculated nitrogen in the feces, and that in anemia functional disturbances of the alimentary canal and kidney do occur which could cause irregularities in the excretion of nitrogen and serve to explain any temporary increase or retention of nitrogen, provided the pathological deviations do not reach too high a degree. In pernicious anemia Mohr³ thinks that we may have a retention of nitrogen in some cases, even on a low nitrogen intake, while in others a loss of nitrogen may occur on a higher intake,

and that the nitrogen exchange is not dependent on the hemoglobin poverty, but controlled by other factors, such, possibly, as the influence of toxic substances which vary in intensity.

In severe anemia, due to *Bothriocephalus latus*, where we have a known toxic action, as shown by Talliquist,⁶ Rosenquist⁴ was able to show a definite loss of nitrogen dependent on the occurrence of the worm in the body, while after its removal a retention was usually found (Bohland² and Vannini² have observed a similar condition in *Anchylostoma* anemia); he thus regards the loss of nitrogen as due to a toxine and not to the anemia, *per se*.

Cases of pernicious anemia can be kept in nitrogen equilibrium on approximately the same small quantities of protein as normal individuals, as shown by Bernert and von Stejskal.²

Partition of Urinary Nitrogen—(a) Urea: Von Noorden¹ noted a "marked reduction of the per cent of urea nitrogen in some cases of pernicious anemia." These cases were in an advanced state and with œdema. He quotes other observations with normal values. Voges^{7a} found this diminution of per cent of urea nitrogen only as an exception. Podoa^{7a} in 1909 believes there is a diminution of per cent of urea nitrogen in all forms of anemia. In experimental pyridin anemia in dogs, Samuely,⁸ in a careful metabolic study, found that as the anemia progressed the urea per cent dropped from 86.3 per cent to 72.14 per cent.

(b) Ammonia: Von Noorden¹ and others find the ammonia normal, or a slight tendency to a relative increase in this disease.

(c) Amino-acid fraction: This fraction has in some instances been found to be increased, though there may be some doubt as to their value, since the determinations were made by older methods. Erben,⁸ in one case, found the amino-acid nitrogen distinctly increased, and Samuely,⁷ in his experimental anæmia, showed a definite rise which he felt might be explained by other causes than the anæmia.

The effect of removal of the spleen on nitrogen metabolism was studied by Noel Paton,⁹ in 1900, on dogs in the form of urea and ammonia. He found no essential difference before and after splenectomy.

Mendel and Gibson¹⁰ in the case of a man with enlarged spleen and secondary anæmia with ascites, following malaria, studied the metabolism after splenectomy, during which period pneumonia developed. Their conclusions are, "analytical data fail to indicate any striking variation from the normal distribution of urinary components which can be associated with the exclusion of the function of the spleen." The nitrogen intake was not studied. Monaczewski^{10a} studied nitrogen metabolism in a case complicated by pneumonia seven months after splenectomy and "no noteworthy variation was seen from that in fevers."

The most valuable work is that of Umber,^{5, 11} who showed in two cases of Banti's disease that there was a pathological destruction of protein and after splenectomy a normal metabolism was established. He explains this on the basis that by removing the spleen we remove the toxic cause. His work is careful in detail, and he emphasizes the necessity for all requirements of a careful balance sheet, for rough methods may not show us the nitrogen loss; moreover, pathological destruction of protein may be overlooked if we allow too high an intake of nitrogen, for then we may find a nitrogen balance as with fever cases, while on a smaller intake, yet sufficient for body needs, this would not occur. "Cases must be studied over several periods to see if there is a toxic destruction of nitrogen," he says. No essential change was found in urea per cent before or after splenectomy in the one case on which it was studied.

In March, 1913, Eppinger,¹² and also Decastello,¹³ first reported the results of splenectomy in pernicious anæmia and since have reported more cases. Also Klemperer and Hirschfeld,¹⁴ von Mosse,^{15a} Huber,^{15a} Port,¹⁵ Harpole and Fox,¹⁶ Coleman and Hartwell,¹⁷ and Moffitt,¹⁸ have reported similar instances, and Türk¹⁹ discusses this procedure. In some cases great benefit has been derived from splenectomy, but of how lasting duration time alone will tell.

A case of pernicious anæmia entered The Johns Hopkins Hospital November 11, 1913. No improvement occurred and splenectomy and direct transfusion were done February 3, 1914, following which daily improvement in her condition has occurred.

A summary of the case is as follows:

Medical numbers, 31704 and 32146; surgical number, 33843. Colored (mulatto), housewife, age 35 years.

FAMILY HISTORY—Negative.

PAST HISTORY—Never ill except from measles, whooping cough and mumps as a child. Habits good.

PRESENT ILLNESS—One year ago, without previous gastro-intestinal disturbance, she began having attacks of "indigestion," which have been increasing in frequency and severity, lasting from one hour to a day, consisting of nausea and vomiting small amounts of food and "bile"-stained fluid. No pain with attacks beyond feeling of pressure of gas "around heart," relieved by belching. Attacks have no definite relation to meals, usually come when tired, also often in the morning before breakfast. Bowels have been regular, but moving twice a day. Stools have appeared normal. For six to eight weeks has had palpitation of heart, also roaring in ears. For four weeks swelling of ankles. In recent weeks has noticed that she is tired easily, and has lost weight—average with clothes 140 lbs.; now 110 lbs. Had to stop work one week ago.

PHYSICAL EXAMINATION (composite by Drs. Thayer, Boggs, Clough, Austrian, F. J. Smith, in November, and G. R. M. in January)—A well developed mulatto woman, fairly nourished, complaining of weakness, appears strikingly pale, with yellow tinge to skin and very pale mucosæ. *Sclera* have icteroid tint. *Pupils* negative. Puffiness about eyes. *Nodes*: cervical enlarged to the size of peas, few small ones under angles of jaws; axillary, inguinal, epitrochlears not felt. *Ears, nose, tonsils, thyroid*, all negative. *Teeth*: slight pyorrhœa; otherwise negative. *Tongue*: a little raw towards base. *Throat* negative save for a few white patches over buccal mucosa. *Thorax* well formed; costal angle a little under 90°. *Lungs* negative. *Heart*: point of maximum impulse not seen; felt in fifth interspace, 8½ cm. to left of mid-sternal line; right border 3-3½ cm. from mid-sternal line in fourth interspace. *Sounds* are regular; at apex first sound muffled, followed by a soft blowing systolic murmur transmitted to axilla and well heard over body of heart, being loudest at pulmonic area, where it sounds rougher. Some months later this murmur was not heard in axilla, otherwise as before. Second pulmonic slightly accentuated.

Pulses: equal, regular, small volume, vessel walls not felt. Blood pressure, systolic 115; diastolic 60 (Tycos).

Rate per minute:

November 11-January 11.....	85-100
January 11-February 3.....	90-110
February 3-February 16.....	105- 90
February 16-April 29.....	80- 90

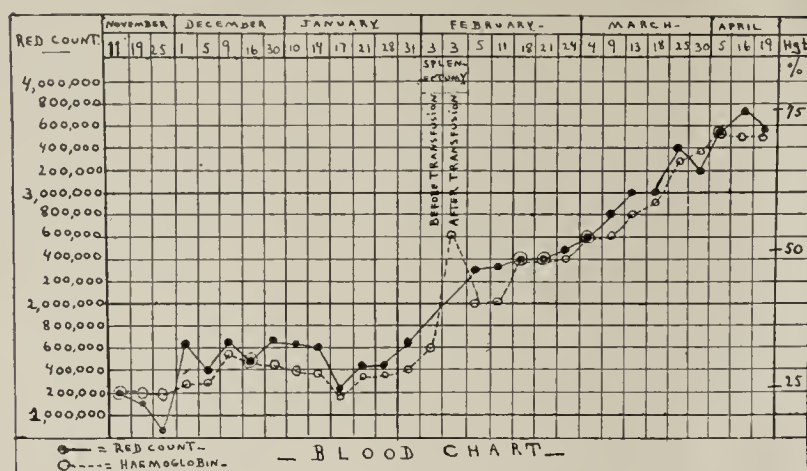
Temperature showed slight daily fluctuations:

November 11-November 29.....	100.0°-99.0° F.
November 29-February 3....	98.0°-99.5° F., rarely to 100° F.
February 3-February 9.....	101.0°-99.0° F.
February 9-February 16....	99.5°-98.6° F.
February 16-March 16.....	98.0°-99.0° F.
March 16-April 29.....	98.6° F.

Abdomen soft relaxed, slight diastasis of recti; intestines or stomach may be seen to descend in region of umbilicus with inspiration. No visible peristalsis. Slightly full in right upper quadrant, generally dull tympany, no tenderness. *Liver* dulness reaches in right nipple line from fifth interspace to 2½ cm. below costal margin, and to 4 cm. above umbilicus in mid-sternal line, where edge is felt, smooth and firm. *Spleen*: edge is just felt at costal margin, firm and rounded. *Kidneys*: right palpable and prolapsed; left is just felt.

Extremities: moderate soft œdema of legs below knees with tenderness over periosteum; otherwise negative. *Reflexes* normal. *Sensation* normal.

Blood: see chart for red count and hæmoglobin. See table for white count, differential counts and blasts. (Drs. Brush, Venable, and Fleming.)



DIFFERENTIAL COUNTS.

	Nov.		Dec.	Jan.				Feb.		Mar.			Apr.
250 white cells counted.....	13	21	2	8	14	22	28	12	17	6	18	30	16
Polynuclear neutrophils.....	52.8	44.4	59.2	66.4	62	54.8	56.8	74.4	64.4	50.3	50	53	65
Eosinophiles.....	.8	.4	.4	1.2	.8	.8	.8	1.6	.4	4.7	2.8	1	2
Mast cells.....	.4	.4	2.4	0	.4	0	0	.4	0	0	1.2	2	0
Small mononuclears.....	27.6	31.2	21.6	29.2	31.2	40.4	34	12	20.8	34.7	26	23	8
Large mononuclears.....	15.6	20.4	12.6	2.8	4	2.8	6.4	5.2	9.2	8.3	14	15	23
Transitionals....	1.6	2.0	1.2	.4	1.6	1.2	2	5.6	5.2	2.0	4	5	2
Myelocytes.....	0	0	1.2	0	0	0	0	.8	0	0	0	1	0
Unclassified.....	1.2	1.2	2	0	0	0	0	0	0	0	2	0	0
Blasts seen in counting 250 white cells.													
Normo.	1	2	4	3	3	4	4	22	?	7	1	0	0
Megalo.	3	7	11	1	3	0	0	0	?	0	0	0	0
White count.....	2740	2640	3400	2960	3960	7320	3800	4890	8400	10200	
	Nov. 11 to Jan. 28, 17 white counts made; extremes = 2300 and 4780.							Feb. 21, 6640 " 24, 7360 Mar. 9, 5610		Mar. 13, 4980 " 25, 8600 Apr. 5, 1200 " 29, 10400			

Seven stained smears and several fresh specimens of blood were studied in the period before splenectomy and all showed essentially the same picture. The red cells appeared full of hæmoglobin, considerable variation in size with many large oval forms, numerous small cells, striking variation in shape, dumb-bell and sickle forms, etc. Some polychromatophilia, at times a few stippled cells. No parasites, a few nuclear particles (Jolly bodies). Plates appeared decreased. Smear of February 17 showed reds as before. Plates strikingly increased over numbers in smears before splenectomy and distinctly above normal. Nuclear particles markedly increased. On February 28 vital staining showed 8 per cent of reticulated red cells.

Smears of March 3 and 30 and April 16 always showed red cells of the type found in pernicious anæmia, but the variation in size and shape became less marked; there was no stippling, and very rarely polychromatophilia and the nuclear particles were somewhat fewer. Fragility of red cells not studied. Coagulation time in November slightly increased; in April normal.

Gastric analysis: (November) stomach of normal size, slightly prolapsed; no stasis. No free HCl in test meal. Acidity 8 per cent deficit. Total acidity 32 per cent; otherwise negative.

Stools: in November, normal except for occasional rare fatty-acid crystals. In January often soft, mushy, with abnormal amount of gas formation and acid reaction, excessive amounts of cellulose at times, not infrequently fatty-acid crystals and soap needles; otherwise negative. After splenectomy, in February and

March often bulky and soft, but with less gas formation; at times a strong alkaline reaction, and at times signs of disturbance of fat absorption, becoming essentially normal in April. (Urobilin and iron not studied.)

Urine: normal to pale color, usually slightly cloudy; specific gravity 1011-1020, acid reaction; *albumin* usually absent, rarely present as a slight trace, except for about ten days following operation, when it was constant; *sugar* absent; *guaiac* negative. Several times in January a faint acetone reaction occurred, associated usually with attacks of nausea. No diacetic; bile negative. *Sediment* consisted only of vaginal debris and a few round cells.

The determination of urobilinogen by Ehrlich's paradimethylamidobenzaldehyde test was made in January some ten times, always with strictly fresh urine, and was found present, though the reaction was not strong. Two days after splenectomy there was a very intense reaction which persisted for three days, and then gradually grew less intense, disappearing by February 18 (15 days after splenectomy) and remained absent, as it did in Hüber's case.

Wassermann reaction: November (Dr. Bloomfield), negative.

Lumbar puncture: January (Drs. Miller and Levy), normal count. Wassermann, Nonne, and gold chloride tests negative.

Calmette Tuberculin test: November (Dr. Levy), 1 per cent and 5 per cent negative.

Phenolsulphonaphthalein renal function test: January (Dr. Snowden), normal.

Levulose tolerance: 100 g. in January taken; none appeared in urine. Vomited following ingestion of 125 g. After splenectomy, in March, 100 g., vomited twice—75 g. taken and none appeared in urine.

Phenoltetrachlorophthalein test for liver function: (Drs. Rowntree and Chesney), January 14, 27 per cent excreted in faeces.

Under treatment of rest for three months in bed, with proper diet and arsenic, the patient showed no improvement, nor did 375 cc. of defibrinated blood given intravenously on November 30 cause any real change in the picture. On January 13 2.5 cc. of whole blood was given without effect.

The case being considered one favorable for splenectomy, she was transferred to the surgical service February 3, on which day Dr. Finney operated. Immediately afterwards Dr. McClure gave a direct transfusion from her husband, who belonged to the same iso-agglutinin group (tested by Dr. Moss).

The patient made a good surgical recovery and held the blood. Though there was no severe hemolytic crisis, her conjunctivæ became yellower and the urobilinogen increased in the urine, lasting for a few days after the operation. She was transferred back to the medical service with all wounds healed, February 15.

Physical examination (Drs. Levy and Clough) at this time revealed nothing new, save that there was less icteroid tint to scleræ than in November. In March the liver border was thought not to be as low as formerly.

Following the operation the patient began to improve daily. She gained weight, the "indigestion" left, and many little aches disappeared as the blood count rose. She was allowed to get up the middle of March and left the hospital April 29, with no yellow tinge to skin or scleræ. At this time, although the blood picture was greatly improved, yet it was still that of a primary anæmia. A letter to Dr. Thayer in June said her condition was as good as when she left the hospital.

To study the nitrogen metabolism, the patient was kept in bed during all observations and given a measured and weighed diet of proteid, fat and carbohydrate in the proportion of about 20, 30 and 50 per cent respectively. Calories were estimated by tables. Her calorie intake was low, 25 per kilo, which is but barely enough for a patient in bed; nitrogen intake was sufficient. There was considerable difficulty in per-

suading her to eat, especially the same amount each day, which has resulted in an undesirable variation of the nitrogen intake. In all instances for twenty-four hours before the days on which the examinations were made the patient was kept on as nearly the same diet as on the days on which the determinations were made, the third day having the greatest variation. Consecutive days were not always obtained, owing to errors of collections. Other days, besides those tabulated, were studied, which tended to show the same results, but are not recorded, as errors in collections or determinations were feared.

The total nitrogen in the food, urine, and stool (dried and powdered) was determined by the Kjeldahl method, two parallel determinations on each specimen, as was also done in determining the ammonia by Folin's older method.²⁰ The urea was determined by Marshall's method,²¹ three samples being tested each time. The results are tabulated.

verse the result. The patient lost weight in the period before splenectomy and was gaining weight in the period after, while the average intake of nitrogen was slightly greater (between test days she was actually eating more than before splenectomy), it does not seem enough to account for the retention.* Of course, it would have been desirable to have determined on high and low intakes of nitrogen what the balance would have been, but this could not be done.

Various possibilities occur to one as to why such a difference might exist; among others, it might be due to the fact, as in Umber's case, that we have removed a toxic cause, or that which allows a toxic cause to exercise its full function: or the loss might be associated with the slight fever, in turn perhaps associated with circulating toxic substances present before splenectomy but not found afterwards at the time when the tests were made; or that we found the patient in one of Rosenquist's periods of nitrogen loss and afterwards in a period of retention.

NITROGEN METABOLISM DATA.

(A) BEFORE SPLENECTOMY.

Date.	No. of day.	Calories per kilo.	Nitrogen intake.	Total Nitrogen output.	Amount of urine.	Nitrogen in urine.	Nitrogen in stool.	Urea in urine.	Urea Nitrogen.	Urea Nitrogen.	Ammonia in urine.	Ammonia Nitrogen.	Ammonia Nitrogen.	Albumin in urine.	Weight of patient.
			gm.	gm.	cc.	gm.	gm.	gm.	gm.	%	gm.	gm.	%		
January 22-23.....	1	25	5.0	6.68	800	6.08	.60	7.2	3.36	54.9	.58	.47	7.7	0	Nov. 16—108 lbs.
" 23-24.....	2	—	—	12.07*	1375	11.24*	.83*	12.04	5.60	50.0	.86	.70	6.1	0	Jan. 21—105 lbs.
" 24-25.....	3	31	6.74	6.91	1125	6.14	.77	7.69	3.58	58.1	.45	.37	6.0	0	
" 28-29.....	4	25	12.9	14.60	2180	14.12	.47	10.46	4.88	34.5	.37	.30+	2.1	Very slight.	
" 30-31.....	5	25	8.75	9.25	1860	8.37	.50	13.40	6.20	74.0	.43	.35	4.1	0	Jan. 30—102 lbs.
Average	—	—	8.34	9.03	1468	8.67	.56	10.15	4.72	54.3	.53	.43+	5.2		

Average Daily Amount of Nitrogen Lost: .78 gm.

*Not in average.

(B) AFTER SPLENECTOMY.

Splenectomy Feb. 3d..															
February 18-19.....	6	25	9.35	7.73	1680	6.49	1.24	10.18	4.75	73.1	.4+	.35+	5.4	0	Feb. 16—101½ lbs.
" 19-20.....	7	25	9.49	7.50	1100	5.85	1.64	10.23	4.77	81.5	.4—	.35	5.9	0	
March 5-6.....	8	25	8.75	8.50	1775	7.54	.96	12.80	6.00	78.8	.5	.41+	5.4	0	
" 6-7.....	9	25	8.59	8.75	1970	7.55	1.20	13.47	6.28	83.2	.58	.47	6.2	0	
" 19-20.....	10	25	8.94	9.96	1900	9.04	.91	15.85	7.39	81.9	.62	.51	5.6	0	
" 21-22.....	11	25	9.42	8.51	1725	7.70	.80	13.10	6.10	79.2	.59	.48	6.2	0	Mar. 22—108 lbs. ?
Average	—	—	9.09	8.49	1691+	7.36	1.12	12.60	5.88	79.6	.51+	.42	5.7		April 6—112 lbs.

Average Daily Amount of Nitrogen Retained: .6 gm.

The total nitrogen output before splenectomy fluctuated daily; this was due to the unfortunate variation in the intake. On the fourth day the high output in urine (14.12 g.) may be associated with the presence of a slight trace of albumin. However, an average of four days, on which the output and intake were determined, tends to show a slight daily loss of nitrogen, .78 g., and each day, except No. 2, in itself shows a loss as much as in Umber's cases of Banti's disease. Yet, with more observations and a more equal amount each day, it might be quite possible to show a gain instead of a loss.

Following splenectomy the daily intake and output over six days (in three periods of two days each about two weeks apart) are more nearly equal each day (the patient being better and more willing to eat as desired). Here the average shows .6 g. of nitrogen retained per day. This is not a very essential change; for the average of a few days, like No. 5, where there was a loss of 1.2 g., or No. 8, where a loss of .25 g. might re-

However this may be, coincident with clinical improvement there appeared a more favorable nitrogen balance.

A low per cent of urea nitrogen in some cases of pernicious anæmia has been spoken of in the literature. In this case on the days before splenectomy it averaged 54.3 per cent, lower than would be expected to correspond with the total amount of nitrogen in the urine, day 4 showing but 34.5 per cent, seems almost as if there must be an error. Again day 5, with output of 8.37 g. of nitrogen, shows 74 per cent urea nitrogen, in itself low, but does not seem to vary in the proportion one would expect, when day 2, with an output of 11.24 g. nitrogen, shows but 50 per cent as urea nitrogen.

On the six days studied after splenectomy the urea per cent averaged 79.6, on an average output of 7.36 g. of nitrogen in

* The stool contained less nitrogen before than after splenectomy; the significance if any, is questionable.

the urine, which is less than the average output before splenectomy (9.19 g., which includes all five days), when the per cent of urea was much lower. Here one is surprised to find a figure as high as 81.5 per cent on day 7, when but 5.85 g. of nitrogen were found in the urine, the other days being about normal. It is possible that the low urea per cent before splenectomy was associated with deranged liver function, as is suggested also by the phenoltetrachlorophthalein test, while after removal of the spleen some change occurred (disappearance of some circulating toxic substance?) which allowed the liver to functionate more normally; or again, following Padoa's work, it might be due to anæmia, *per se*, the change associated with improvement.

No changes or abnormalities were noted in the ammonia of the urine.

Richet,²² as a result of his studies of splenectomized dogs on which for a period of two years their daily intake of food and their body weight were studied, concludes that the spleen exercises a function on nutrition, for after splenectomy the dogs ate more food to keep up their body weight. This might suggest that after splenectomy a loss of nitrogen would occur on the same diet that before splenectomy allowed nitrogenous equilibrium. As far as one can judge from the data obtained in the case of pernicious anæmia this would not hold true. We are, however, dealing here with a pathological condition of man and not with normal dogs.

It does not seem justifiable to draw conclusions on the normal function of the spleen from the study of cases where this organ has suffered pathological changes.

To conclude, in a case of pernicious anæmia showing no improvement for three months, splenectomy was performed, after which the patient's general condition and blood picture improved. Coincident with this improvement the urobilinogen disappeared from the urine, a more favorable nitrogen balance occurred, and a rise in per cent of urea nitrogen, which previously had been below normal.

It is a great pleasure to acknowledge my indebtedness to Dr. Thayer, whose suggestion it was that some metabolic studies be made in this case, and under whose supervision this work was performed; to Dr. J. H. King for many helpful suggestions in carrying out the work, and to Dr. R. R. Snowden for aid in technic.

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NOTES ON NEW BOOKS.

Materia Medica, Pharmacology and Therapeutics. Prescription Writing. By WALTER A. BASTEDO, Ph. G., M. D., etc. Illustrated. (Philadelphia and London: W. B. Saunders Company, 1913.)

This book of 559 pages is an adaptation for the most part of lectures delivered at Columbia University by Dr. Bastedo. It is inclined to be elementary in character and is essentially a textbook on pharmacology for the students.

In the preface the author states that he has not attempted to compile extensive bibliographies but he refers to certain works on pharmacology and physiology which he has freely consulted. The book does not impress one as the outgrowth of first-hand knowledge gained from personal experimental work or from thorough familiarity with original sources. The author is inclined to be dogmatic and has not always exercised good critical judgment, accepting much as proven where reasonable room for doubt still exists. Certain theories are accepted at times as the true explanation of certain phenomena and not simply as theories. As a pharmacology the book does not fill a definite need.

Infections of the Hand. By ALLEN B. KANAVAL, M. D. Second Edition. Thoroughly Revised. Illustrated. (Philadelphia and New York: Lea & Febiger, 1914.)

The importance of this work to all surgeons was noted in its first appearance in the BULLETIN, and it is unnecessary to do more than call attention to the second edition, which has given the author an opportunity to add to its value by fuller detail along certain lines. Surgical internes and students, working in dispensaries, could not do better than study this book thoroughly, for in infections of the hand much bungling surgery is constantly exhibited.

Time and the Timeless—Songs of Shadow and of Hope. By a PHYSICIAN. 2/6. (London: Henry J. Glaisner, 1914.)

While these verses from a physician cannot be ranked with those of Holmes or Weir Mitchell, yet this small, neatly printed volume deserves to be placed on the same shelf as those of these authors, for the poems are of more than usual merit. They exhibit deep religious feeling and while they are of shadow, the

shadow is lit by hope. They are the work of a serious thinking man of high ideals, and whereas the author's thoughts are not rare, his expression is pleasing and will be attractive to many by its simplicity and sincerity. The introductory verses are symbolic of the author's attitude of mind.

A few stray flowers of song
Found in my garden. Call them only weeds,
But Nature sowed the seeds,
And unto her do they belong.

She fed them, while men slept, with smiles and tears
And they have flourished there.
I would it were an offering more fair,
Fitter for human needs,
Mixed with the sterner harvests of the years.

A verse to stimulate us all runs as follows:

We act ourselves:
And in the actions, as in a mirror, shine
Our features line by line,
And if we bend our wills to better deeds,
We hope to trace
In them a nobler face.

Black's Medical Dictionary. By JOHN D. COMRIE, M. A., B. Sc., M. D., F. R. C. P., Edinburgh, Lecturer on History of Medicine, University of Edinburgh; Lecturer on Clinical Medicine, University of Edinburgh, etc. Fifth edition, completing thirty thousand, containing 431 illustrations in the text, etc., and 12 plates in color. (New York: The Macmillan Company, Publishers, 1914.)

This book of nearly 860 pages is not so much a medical dictionary in the opinion of the reviewer as a dictionary of medicine, modelled somewhat after the manner of Quain's dictionary. It is not compiled so much to assist the medical student to acquaint himself with the meaning of the words which he finds in his text-book and journals as to render it possible for "district nurses, teachers, clergymen and professional men generally, ship-captains, colonists, business men and others" to know something of medicine and possibly, although it is not so stated, to practice the healing art in an emergency. It contains special directions for the treatment of accidents, for methods of recovery from drowning; for the treatment of fits and convulsions; for poisoning; for unconsciousness whether from alcoholism, apoplexy, opium poisoning or uræmia; and for the preservation of health by exercise, diet, ventilation and general sanitation.

It presents also the symptoms of disease, gives directions as to nursing and the management of children. It further treats of the action of medicine and of physiological matters such as circulation, perspiration, respiration, temperature, pain, sleep and vision.

The work is carefully and painstakingly written and seems fairly well abreast of modern discoveries in medicine. At the same time a glance at its pages gives one an impression that it is too much a treatise on practice and yet not specific enough to be of the highest utility. To the ship-captain and colonist it may be of real service, in default of any other medical aid; to the clergyman or amateur physician where skilled medical attendance is available, it presents too much information which may prove a stumbling block and delay adequate treatment.

The colored illustrations are well done. By a curious lack of consistency, colored pictures of chicken-pox, German measles, measles and scarlet fever are presented but there is no representation of small-pox, which is equally apt to break out in remote regions and give rise to more serious epidemics.

Sanitary topics such as water supply, ventilation, disinfection, water-closets, and sewage removal are very well written. The book as indicated above has a limited range of usefulness and will evidently fill a recognized want in isolated communities.

Diseases of Women: Medical and Surgical Gynecology. By CHARLES A. L. REED, M. D. Illustrated. \$6. (New York and London: D. Appleton & Co., 1913.)

In this octavo volume of 872 pages of text—minus a very considerable amount of space allotted to illustrations—the author undertakes to discuss not only those topics usually treated in books of this size on gynecology, but also surgery of the urinary system, rectum and breast, as well as certain major obstetrical operations. Furthermore, the work is offered as fulfilling the requirements of a text-book for undergraduate students, a teacher's reference book and a guide, both medical and surgical, for the practitioner.

The inevitable result is, of course, the production of an incomplete and epitomized presentation of the various subjects treated.

But the fact that the book falls short of its author's aim does not seriously detract from the very considerable degree of merit it possesses. Indeed, it reflects distinct credit upon the writer since it contains a wealth of accurate information which has been wisely selected, logically arranged and tersely presented with clearness and force. The subject matter is divided into sections on malformations, injuries, displacements, foreign bodies, infections, neoplasms, trophic changes, obstetrical operations and menstruation; the subdivisions being made on an anatomic basis.

It is to be deplored that no mention is made of certain live and important gynecological subjects. Notably, vaccines in the diagnosis and treatment of gonorrhœa; the Roentgen and radium treatment of neoplasms and other gynecological affections; and the recent complete revision of our knowledge and views regarding menstruation following upon the work of Hitschmann and Adler.

On the whole the author's advice is sound and in accord with present-day teaching, but the radical operative treatment advocated in cases of puerperal infection would not be generally endorsed either in this country or Germany.

The numerous illustrations are for the most part sketchy and often semi-diagrammatic, but are of material aid in conveying the author's ideas.

Some American Medical Botanists, Commemorated in our Botanical Nomenclature. By HOWARD A. KELLY, M. D., LL.D. Delivered as a lecture before the Medical Historical Society of Chicago, 1910, and before the University of Nebraska, 1913. (Troy, New York: The Southworth Company, Publishers, 1914.)

This tribute by a medical botanist to men who have given their names, talents and energy to the science of Botany is graceful and timely. The volume contains more or less complete sketches of the lives and attainments of thirty medical men. A large number of them were immigrants to America in pioneer days; such men as Michel S. Sarrazin, a native of France who emigrated to Quebec at the age of 26 years and gave his name to the beautiful pitcher plant, the *Sarracenia purpurea*; John Mitchell, a native of England but a resident of Virginia, from whom the familiar checkerberry, *Mitchella repens*, received its name; Cadwalader Colden, a native of Scotland but a resident of New York later, where he was a physician, Surveyor-General of the State and Lieutenant-Governor and ultimately a botanist, a friend of Linnaeus, who named after him a new genus of plants known as *Coldenia*; John Clayton, of England, who came to Virginia as a youth and from whom *Claytonia Virginia* or *Spring Beauty* received its botanical name; others like John Bartram, Alexander Garden, Adam Kuhn, Moses Marshall, Caspar Wistar and Benjamin Barton were descended from recent immigrants and enriched the new science by their enthusiastic labors; while others like David Hosack, Asa Gray, John Torrey and Charles W. Shert

seemed more nearly products of the soil. The life story of all is well told but proves quite too brief and the reader laments that concerning many of them such meagre facts are alone available. There are interesting stories of daring adventures in the wilds of a new country in search of new plants and thrilling tales of quests to establish the correctness of the discoveries of other botanists. No one can read without a thrill of the quest of Gray and others in search of *Shortia*, lost for ninety-eight years and finally rediscovered in 1886 near the exact spot where it was first discovered by Michaux!

The book is profusely illustrated by excellent reproductions of old prints and is beautifully printed. The original lecture referred to upon the title page is contained in a scholarly Introduction which contains much interesting information as to the names of plants ancient and modern. The book is most creditable to the author, who has achieved deserved success in many other fields.

Flies in Relation to Disease—Non-Bloodsucking Flies. By G. S. GRAHAM-SMITH, M. D., University Lecturer in Hygiene, Cambridge. (Cambridge: At the University Press, 1913.)

This volume is one of the Cambridge Public Health Series, prepared under the editorship of Dr. G. S. Graham-Smith and Mr. J. E. Purvis. It is a useful and timely publication at a time when the agency of flies in conveying disease is beginning to be appreciated in every country. The work contains chapters on the life history of the fly, his anatomy, habits, and methods of carrying and distributing bacteria, etc., which are clear and admirably illustrated. These are followed by chapters on the relation of flies to specific diseases like typhoid fever, epidemic or summer diarrhoeas, cholera, tuberculosis, anthrax, and bacterial diseases like diphtheria, ophthalmia, plague and staphylococcal infections. It is of interest to note, as indicating the judicial character of the work, that the author does not seem to regard it as proven that the housefly is to any great extent a carrier of the typhoid bacillus under the ordinary conditions of city life, but inclines to the belief that he may play an important part in the direct transmission of this disease from infected typhoid patients to healthy persons in the unsanitary conditions of camp life. He believes, however, that the whole subject needs to be restudied and his attitude of mind suggests the suspicion that the domestic fly has been unduly condemned. He points out the fact that so-called typhoid carriers are much more worthy to be censured for the spread of the disease. The work will be of great value to sanitarians and health officers.

Treatment of Neurasthenia. By DR. PAUL HARTENBERG. Translated by ERNEST PLAYFAIR, M. B., M. R. C. P. (Edinburgh, Glasgow and London: Henry Frowde and Hodder & Stoughton, Publishers. 1914.)

This admirable little book of 283 pages is the sequel of a previous work by the author, "The Psychology of Neurasthenia"; it relates to treatment and cure. As the work represents the results of one who has spent many years in the treatment of this class of invalids, it is of value to all who attempt to treat one of the most intractable and discouraging of functional diseases.

The author's definition of neurasthenia follows closely the common idea that it is a state of simple depression of the nervous system and is quite as satisfactory as Polonius' definition of madness—and no more illuminating. What produces the condition, whether an exhaustion of the nerve cells or an intoxication, he does not know. He finds a condition and has no adequate theory to explain it satisfactorily. He regards it a physical and material affection, but does not explain why. He asserts, however, that it is not purely imaginary or fictitious.

To treat this condition, its causes must be discovered and eliminated. The chapters on treatment are full and give detailed

methods to be pursued. He shows in what manner every neurasthenic should be studied and gives rules for both general treatment and special treatment of the individual predisposition, the exciting causes, such as dyspeptic symptoms, organic affections like gout, diabetes, arterio-sclerosis, infectious diseases like typhoid fever or influenza, dilated stomach, overwork or emotive causes. In the treatment of the fundamental asthenia he uses principally the preparations of strychnia by hypodermic injections, although a variety of other nerve tonics is mentioned. The mental state must be met by the direct personal influence of the physician, whose duty it is to give encouragement and mental stimulation to those who have lost all power of self-direction. He also believes that the application of general electricity is of service.

His methods are carefully thought out and will prove of great service to physicians who see early cases of neurasthenia in general practice. It is not an epoch-making work, but none the less a useful one.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by HOBART AMORY HARE, Professor of Therapeutics, etc., in the Jefferson Medical College, Philadelphia, assisted by LEIGHTON F. APPLEMAN, M. D., Instructor in Therapeutics, Jefferson Medical College. Volume II, June, 1914. Hernia Surgery of the Abdomen, Exclusive of Hernia, Gynecology, Diseases of the Blood, Diathetic and Metabolic Diseases, Diseases of the Spleen, Thyroid Gland, Nutrition and the Sympathetic System, Ophthalmology. The authors of the sections on Hernia and Surgery of the Abdomen are Drs. W. B. COLEY and JOHN C. A. GERSTER, of New York; on Gynecology, Dr. JOHN G. CLARK of Philadelphia; on Diseases of the Blood of the Ductless Glands of the Sympathetic System and Diathetic and Metabolic Diseases, Dr. ALFRED STENGEL; and on Ophthalmology, Dr. EDWARD JACKSON. (Philadelphia and New York: Lea & Febiger, 1914.)

The articles are in the nature of analytical and critical reviews and they contain the results of the latest work. They are too long and detailed for a fuller review, but are none the less deserving of the careful reading of physicians who desire to keep themselves informed of the progress of medicine and surgery. The series has been in progress for many years and its value is shown by the liberal patronage which it has secured.

Life and Letters of Nathan Smith, M. B., M. D. By EMILY A. SMITH. With an introduction by WILLIAM H. WELCH, M. D., LL.D. (New Haven: Yale University Press, 1914.)

This book has a double interest because it not only is a fitting contribution to the celebration of the Centennial Anniversary of the "Medical Institution of Yale College," of which Nathan Smith was an organizer and chief ornament, but also by reason of his profound influence upon medical education in New England and his connection with Jefferson Medical College in Philadelphia and the University of Maryland in Baltimore, through his son, Prof. Nathan R. Smith, who filled so large a place in the medical annals of Maryland, and indirectly through his grandson, Dr. Alan P. Smith, associated with the University of Maryland as a teacher and later as a trustee of The Johns Hopkins Hospital and of The Johns Hopkins University during the critical period of the foundation and organization of these institutions, which have influenced widely both general and medical education.

It has been a labor of love on the part of Mrs. Alan P. Smith to make a substantial addition to our knowledge of Nathan Smith by the publication of his interesting and hitherto unknown letters to Dr. Shattuck, of Boston, and of extracts from his lectures and writings. She has also given a charming account of early pioneer

conditions in New England during the last quarter of the eighteenth century, and of the struggles and privations which accompanied early efforts to establish medical schools.

On the personal side, to quote the words of Dr. Welch: "We catch intimate glimpses of the active-minded lad upon the frontier, of the student at home and abroad getting, in spite of great difficulties, a good medical training; of the lover 'transported with joy and expectation'; of the devoted husband and father solicitous for the education of his sons; of the busy physician and surgeon 'bandied about from one part of the country to the other,' treating fevers, couching for cataract, cutting for stone, excising tumors, and embarrassed most of the time, as is the way of doctors, from failure or inability to collect his fees, small as they were; of the founder of medical schools and the professor filling, and filling well, all the chairs in the medical curriculum, from all accounts a great teacher—and withal deserving President Woolsey's characterization of him as 'the most delightful, unselfish and kind-hearted man I ever knew and we children loved him.'"

He was indeed a great man and his characteristics are charmingly brought out in this all too-brief biography. The book is finely printed and well-illustrated by reproductions of photographs and facsimiles of original documents. It reflects great credit upon the publishers and upon the author.

The growing interest in historical medical topics lends the hope that it may be widely read and appreciated.

Auricular Flutter. By WILLIAM T. RITCHIE. (Edinburgh and London: W. Green & Son, 1914.)

The study of cardiac disease, especially the analysis of the arrhythmias has been advanced so rapidly by the use of graphic methods of registration, that most text books on the subject do not include all of them. In this small volume of one hundred and thirty pages the author has given an excellent résumé of a type of cardiac irregularity, only recently differentiated. While the experiments and clinical observations along this line are of great importance in developing the knowledge of the different forms of tachycardia and arrhythmia of the heart, so many of the fundamental points of auricular flutter are as yet unsettled, that any book written upon the subject may still be somewhat unsatisfactory.

The first chapter of the book is devoted to an excellent summing up of the anatomy and the normal and pathological physiology of the heart as shown by the various means of registration. This short review covers most the elementary features of cardiac irregularities and prepares the reader for the more complex subject that follows. In the remainder of the volume the condition termed auricular flutter is discussed in detail, both from the clinical and experimental standpoint. It is well supplemented by numerous curves and the histories of all such cases reported in the literature. The bibliography is very complete and the book as a whole can be commended as an excellent means by which one may become acquainted with the newer details of cardiac disease.

Tuberculosis: Its Cure and Prevention. (A book for laymen.)

By EDWARD O. OTIS, M. D. (New York: Thomas Y. Crowell Company, 1914.)

A very satisfactory presentation of the important facts about the cause, prevention and cure of tuberculosis. The book is clearly and agreeably written. Though designed for laymen, it contains important material with which every physician should be acquainted. Medical students will profit by it.

Ten Sex Talks to Boys Ten Years and Over. By I. D. STEINHARDT, M. D. Price \$1. (Philadelphia and London: J. B. Lippincott Company, 1914.)

Most physicians with some experience of the difficulties of the period of development will agree that much unnecessary distress and nervousness is caused by the conventional attitude of silence

with regard to the vital topics discussed in this book. Juvenile curiosity is officially ignored, the topic of sex is taboo: the resultant compromises are often disastrous. This situation forms an organic part of the structure of modern social thought and its modification can only be a matter of slow evolution.

The author pays little attention to the complexities of the question; to him the solution appears to be to place before the developing youth a simple statement of the facts of the sexual life. As to his formulation of the facts little exception need be taken; the tone of the book is, however, essentially hortatory, and reminiscent of the prohibitionist, and one may doubt the wisdom of making the flesh of the youthful auditor creep by such discussions as those on syphilis, gonorrhœa and masturbation. If the author has not struck the right key-note, at least he is in earnest, and there may be situations where the best available solution is to place such a book in the hands of a boy of ten years or over.

Feeble Mindedness: Its Causes and Consequences. By HENRY HERBERT GODDARD, Ph. D. Pp. XII + 599. Price \$4.00. (New York: The Macmillan Company, 1914.)

In this volume the author publishes the very valuable material which he has been accumulating at the Training School at Vineland, N. J. In the opening part he discusses the general problems of feeble-mindedness, and outlines his methods of investigation. He then presents in a brief form the case histories of 327 cases of feeble-mindedness. In the report and discussion of these cases emphasis is laid on the family history, while the clinical history of the individual is of the most meager description. This no doubt is partly due to the nature of the material, but it also represents the attitude of the author towards the whole question. In the absence of adequate clinical data a solution of the individual case will never be found by shaking the family tree, however vigorously, and the accumulation of more material is not so much required as the study of cases whose personal histories have been worked over much more intensively. In the presence of a neuropathic ancestry Goddard pays little attention to a positive Wassermann reaction; he discusses in a general statistical way questions which are only to be answered by accurate anamneses and clinical examination. After presenting his case histories the author discusses a variety of questions. He tends to the opinion that the inheritance of feeble-mindedness obeys the Mendelian law and that feeble-mindedness behaves as a unit character.

In the concluding chapters various practical aspects of the problem of feeble-mindedness are discussed and its relations to pauperism, alcoholism, prostitution and crime are emphasized. Goddard admits that the pressure of the popular demand has caused him to publish his material in a form which is far from complete and it is to be regretted that the author's critical judgment did not withstand this pressure.

The book as a whole is extremely interesting and the material being presented in a somewhat popular form it may be considered a good introduction to the problems presented by the feeble-minded.

Archives of Neurology and Psychiatry, from The Pathological Laboratory, London County Asylums. Edited by F. W. MOTT, M. D., F. R. S., F. R. C. P. Vol. VI. (London: John Bale, Sons & Danielsson, Ltd., 1914.)

It is always a great pleasure to welcome a new volume of the Archives of Neurology and Psychiatry. The present volume may not be quite so well-balanced as some of its predecessors, but it contains many interesting and important papers.

In discussing "The Nature of the Condition termed Parasyphilis," Dr. Mott reviews the evidence which led up to the idea that general paralysis was definitely due to the syphilitic organism, and following the researches of Noguchi and Moore he has been able to demonstrate the specific organism in sixty-six per cent of his cases.

In another paper on the occurrence of general paralysis in the London County Asylums, it was found that fifteen per cent of the male admissions were suffering from that disease. On account of such a state of affairs, a strong plea is put forward for the prevention of the cause of the disease and to show how frequently the nervous system may be affected, the following appalling statistics are recorded:

In Vienna out of 4134 officers infected with syphilis 198 subsequently suffered from general paralysis, 116 developed locomotor ataxia, and 134 developed cerebro-spinal syphilis.

Candler and Mann contribute an article on "The Wassermann Reaction in the Diagnosis of Mental Disorders." This work has been most carefully done and their results correspond closely to those obtained by other workers. They have, however, in addition carried out an interesting series of tests on the cerebro-spinal fluid and blood serum obtained post-mortem and conclude that "On any case in which a clear cerebro-spinal fluid or a serum showing no hæmolysis can be obtained post-mortem, the Wassermann test on these fluids may be taken with reliance."

Within recent years Dr. Mott had interested himself greatly in the relationship of heredity to insanity and three valuable contributions to the topic are made by Drs. Mott, Wilson White, and Wooten.

Dr. Edgar Schuster has a paper on "Hereditary Resemblance in the Fissures of the Cerebral Hemispheres." A most careful description is given of the brains of a mother and daughter, and of two brothers. He also contributes a description of the convolutional pattern of the brain of a Malay.

Comparative neuro-biology is represented by a most painstaking and careful paper by Fortuyn on the cortical cell lamination of the hemispheres of some rodents. Most excellent photographs and diagrams accompany these papers.

In the appendix a series of papers is incorporated which have been previously published. Of these special mention may be made of Dr. Mott's excellent paper on "The Relation of Head Injury to Nervous and Mental Disease," and an interesting account of fatal pellagra in two English boys in which the histo-pathological findings of one case are compared with the histological changes in the nervous system found in a case of pellagra dying in the Abassieh Asylum, Cairo.

There are several other interesting communications, but the above may serve to give some idea of the scope of the present volume.

Spectrum Analysis Applied to Biology and Medicine. By C. A. MACMUNN. Pp. 110. Price \$1.75, Net. (Longmans, Green & Co., 1914.)

This small volume is an epitome of the author's researches on the spectrum analysis of the pigments, a book written between attacks of illness and based on work which was conducted after the routine activities of the day were done. Obviously the book will find favor chiefly in the hands of those trained in the difficult science of spectrum analysis and those who use this in the biological study of the pigments such as are found in the animal and vegetable kingdoms. A short introductory chapter deals with the historical side of the spectrum, the instruments used, the nature and significance of the Fraunhofer lines and the various kinds of spectra. The chapter on the "General Chromatology of Plants and Animals" is extremely interesting and includes some of the chemistry of the pigments in general. Chlorophyll, hemaglobin and its derivatives are well discussed and their characteristic spectra given in charts. The section on "Quantitative Spectrum Analysis" can only be understood by the mathematician and physicist. A useful bibliography finishes the work. The book is simply written, free from all garnishes and will doubtless prove stimulating to those who work in this highly specialized field of physical biology. Moreover it will always serve as a ready guide for those about to enter upon this particular type of research.

On Dreams. By PROF. DR. SIGMUND FREUD. Authorized English Translation by M. D. EDER. With an Introduction by W. LESLIE MACKENZIE. \$1.00. (New York: Rebman Company.)

Dr. Mackenzie in his introduction to this little volume hits the nail on the head when he criticizes the fact that most text-books on insanity do not attempt to show how mental diseases have their roots in the mental processes of the normal mind, but usually content themselves with a purely descriptive and symptomatological statement regarding the disease process. Freud's genius in elaborating the theory of psychoanalysis and of dream interpretation has happily changed that state of affairs, and has instilled new life into the study of the neuroses and psychoses.

In this short essay of 106 pages Freud lucidly and clearly sets forth his ideas in regard to the interpretation of dreams.

The book in no way replaces Freud's more elaborate work, "Die Traumdeutung," but it may serve as a useful introduction and stimulus to the larger and more comprehensive work.

Surgery: Its Principles and Practice. For Students and Practitioners. By ASTLEY PASTON COOPER ASHURST, A. B., M. D., F. A. C. S. Instructor in Surgery in the University of Pennsylvania, Associate Surgeon to the Episcopal Hospital, and Assistant Surgeon to the Philadelphia Orthopaedic Hospital and Infirmary for Nervous Diseases. With 7 Colored Plates and 1032 Illustrations in the Text, Mostly Original. (Philadelphia and New York: Lea & Febiger, 1914.)

The book is divided into three main sections: General Surgery, Systemic Surgery, Regional Surgery. In the preface the author says: Emphasis is placed on the underlying principles and pathogenesis, diagnosis and indications for treatment. The more important operations are described in detail. The specialities of the eye, the ear, the nose, and the throat are not included. Genito-urinary surgery, gynecology and orthopedics are discussed only so far as they come within the province of the general surgeon. To economize space the bibliographical references are omitted, but the dates of authoritative contributions are indicated and in this way the original references may easily be found. The illustrations are for the most part new, and are well selected. The arrangement of the chapters is good and the text is well written. It might be mentioned that some of the subjects seem to be considered too briefly to be of any value to a beginner in surgery. On the whole the book is an excellent one and should be well received.

1. *Modern Surgery: General and Operative.* By JOHN CHALMERS DaCOSTA, M. D., etc. Seventh edition, revised, enlarged and reset. Illustrated. \$6.

2. *Infant Feeding.* By CLIFFORD G. GRULEE, M. D., etc. Second edition. Illustrated. \$3.

3. *Psychoanalysis: Its Theories and Practical Application.* By A. A. BRILL, M. D., etc. Second edition, thoroughly revised. \$3.00.

(Philadelphia and London: W.B. Saunders Company, 1914.)

These new editions are all valuable and can be warmly recommended to the profession. DaCosta's Surgery is only one of many on the market, but one of the best, and one that a real student of the art will find especially interesting, as the author frankly acknowledges his indebtedness to his predecessors and associates, quoting them and their words frequently, and so leading the reader back to original sources.

Grulee has not modified his book essentially, but gives the latest information to be had on questions of digestion that are being actively studied by many workers.

Brill has introduced new chapters and a glossary into his work, and in other ways also has made it more useful as a practical work.

Thomas Shortt. By ARNOLD CHAPLIN, M. D. Price 2s. (London: Stanley Paul & Co., 1914.)

This book contains a biography of Doctor Thomas Shortt, principal medical officer in St. Helena, and short biographies of some other medical men associated with the case of Napoleon from 1815 to 1821.

Written in the same fluent style as "The Illness and Death of Napoleon" by the same author, this work is most interesting and throws many side-lights on the trials and troubles of the medical advisors of Napoleon during his last illness.

Besides Thomas Shortt, short biographies are given of Doctors Geo. Henry Rutledge, Walter Henry, James Roche Verling, Archibald Arnott, Barry O'Meara, Francis Burton and Alexander Baxter.

Principles of Surgery. By W. A. BRYAN, A. M., M. D. Professor of Surgery and Clinical Surgery at Vanderbilt University, Nashville, Tennessee. Original Illustrations. (Philadelphia: W. B. Saunders Company, 1913.)

The volume is divided into 47 chapters in which the principles of surgery are thoroughly covered. The descriptions are short and clearly written. The book is well printed and the illustrations are good. The student and physician will find this up to date work a valuable help in the way of sound, practical surgical principles.

Health Through Diet. By KENNETH G. HAIG, L. R. C. P. (Philadelphia: J. B. Lippincott Company, 1914.)

Health, according to the writer, is to be obtained and secured by a uric-acid-free diet. We wish the problem were as simple as it seems to Dr. Haig, but that uric acid is such a powerful poison to the system, as is implied by him, is not generally conceded by other students of metabolism, and the author's work is founded only on personal experience. While such experience has value, yet it cannot take the place of experimental work on digestion, and Dr. Haig's statements lack convincing force. As a contribution to medicine the book has but little value.

Pathfinders of Physiology. By J. H. DEMPSTER, M. D. (Published by the Detroit Journal Company, 1914.)

This is a series of sketches, which may serve as a guide to students who are interested in studying the history of physiology. It is but a small volume of light but readable character. This volume cannot take the place of the classic work on this subject by Sir Michael Foster, which has been most inspiring to all students. It is to be hoped that Dr. Dempster's little book may lead the reader to more extended studies.

How to Diagnose Smallpox. By W. MCC. WANKLYN, M. R. C. S., etc. \$1.50. (New York: Paul B. Hoeber, 1914.)

There is much of value to the student in this small volume. The author presents his subject in an unfortunate style, but his experience has been large, and what he says is well worth reading; he does not lay much stress on the almost classical symptoms of pain in the back, the shotty feel of the papules, and the fact that all the papules show at any one moment but one stage of development, but lays more stress on the distribution and nature of the primary rash. There is no doubt that these latter points are very important. As a brief presentation of the subject the book offers many points of interest.

Map Scheme of the Sensory Distribution of the Fifth Nerve (Trigeminus) with its Ganglia and Connections. With Text. \$8. By L. HEMINGTON PEGLER. (New York: Paul B. Hoeber, 1914.)

In colors, well designed and mounted on heavy cloth, this large folding map, 48 by 56 inches, would be serviceable if not bound into covers. It could then be used satisfactorily on the wall of a class room. As it is, it is unhandy and cannot be conveniently referred to.

Ambidexterity and Mental Culture. By H. MACNAUGHTON-JONES, M. D. 75 cents. (New York: Rebman Company, 1914.)

This book on a neurological topic by an obstetrician can lay little claim to scientific value, but is rather a rambling plea for the training of children in the equal use of the two hands, the plea being supported by the opinions of several authorities and extended by a quite irrelevant chapter on the Montessori method.

Diseases of the Skin. By GEORGE THOMAS JACKSON, M. D. 7th Edition. Price \$3. (Philadelphia: Lea & Febiger, 1914.)

This new edition of Jackson's work appears with a marked change in binding, from a dark green to an aggressive red. This prepared us for a thorough revision of the contents, and we were not disappointed.

Much useless matter has been omitted, and new sections on fifteen diseases incorporated, in addition to revision of many old sections; which brings the book up to date.

Along special line of treatment, the author has been fortunate in securing the methods of men eminent in their line of work.

Quite valuable additions are two colored plates and sixteen very good half tones, but there remain a number of illustrations which serve no purpose, and should be replaced by others. The value of the book is greatly enhanced by the very thorough revision.

BOOKS RECEIVED.

A Mind Remedy. By John G. Rayerson, M. D. 1914. 16°. 82 pages. The Quinn A. Boden Company, Rahway, N. J.

American Association for Study and Prevention of Infant Mortality. Transactions of the Fourth Annual Meeting, Washington, D. C., November, 14-17, 1913. 1914. 8°. 447 pages. Franklin Printing Company, Baltimore.

Surgery. Its Principles and Practice. By Astley Paston Cooper Ashhurst, A. B., M. D., F. A. C. S. With 7 colored plates and 1032 illustrations in the text, mostly original. 1914. 8°. 1141 pages. Lea & Febiger, Philadelphia and New York.

A History of Laryngology and Rhinology. By Jonathan Wright, M. D. Second edition, revised and enlarged. 1914. 8°. 357 pages. Lea & Febiger, Philadelphia and New York.

Arteriosclerosis. A Consideration of the Prolongation of Life and Efficiency after Forty. By Louis Faugères Bishop, A. M., M. D. 1914. 8°. 383 pages. Henry Frowde, London; Hodder & Stoughton, London; Oxford University Press.

Guide to the Microscopic Examination of the Eye. By Professor R. Greeff. With the co-operation of Professor Stock and Professor Wintersteiner. Translated from the third German edition by Hugh Walker, M. A., M. B., C. M. [1913.] 4°. 86 pages. The Ophthalmoscope Press, London; Paul B. Hoeber, New York.

Asthma and its Radical Treatment. By James Adam, M. A., M. D., F. R. F. P. S. With four illustrations. 1913. 12°. 184 pages. Paul B. Hoeber, New York.

- The Evolution of the Study of Anatomy and its Important Relation to the Development of Surgical Knowledge.* By J. Ewing Mears, M. D., LL. D. 1914. 8°. 26 pages. Philadelphia.
- Pathfinders of Physiology.* By J. H. Dempster, A. B., M. D. 1914. 8°. 66 pages. The Detroit Journal Company.
- How to Diagnose Smallpox.* By W. McC. Wanklyn, B. A. Cantab., M. R. C. S., L. R. C. P., D. P. H. With illustrations. 1914. 8°. 104 pages. Paul B. Hoeber, New York.
- The Midwife in England.* Being a Study in England of the Working of the English Midwives Act of 1902. By Carolyn Conant Van Blarcom, R. N. With an introduction by J. Clifton Edgar, M. D. December, 1913. Prevention of Blindness, No. 13. 8°. 140 pages. New York City.
- Map Scheme of the Sensory Distribution of the Fifth Nerve (Trigeminus) with its Ganglia and Connections.* By L. Hemington Pegler. With text. 1913. Baillière, Tindall and Cox, London; Paul B. Hoeber, New York.
- The Road to a Healthy Old Age.* Essays Lay and Medical. By Thomas Bodley Scott. 1914. 16°. 104 pages. Paul B. Hoeber, New York.
- Monographs on Biochemistry.* Edited by R. H. A. Plimmer, D. Sc., and F. G. Hopkins, M. A., M. B., D. Sc., F. R. S. *The Simpler Natural Bases.* By George Barger, M. A., D. Sc. 1914. 8°. 215 pages. Longmans, Green & Co., London, New York, Bombay and Calcutta.
- Health Through Diet.* A Practical Guide to the Uric-Acid-Free Diet. Founded on Eighteen Years' Personal Experience. By Kenneth G. Haig, L. R. C. P., Lond.; M. R. C. S., Eng. With the Advice and Assistance of Alexander Haig, M. A., M. D., Oxon. 1914. 12°. 227 pages. J. B. Lippincott Company, Philadelphia; Methuen & Co., Ltd., London.
- The Ready Reference Hand-Book of Diseases of the Skin.* By George Thomas Jackson, M. D. With 115 illustrations and 6 plates. Seventh edition, thoroughly revised. 1914. 12°. 770 pages. Lea & Febiger, New York and Philadelphia.
- Psychoanalysis: Its Theories and Practical Application.* By A. A. Brill, Ph. B., M. D. Second edition, thoroughly revised. 1914. 8°. 393 pages. W. B. Saunders Company, Philadelphia and London.
- Modern Surgery, General and Operative.* By John Chalmers DaCosta, M. D., LL. D. Seventh edition, revised, enlarged and reset with 1085 illustrations, some of them in colors. 1914. 8°. 1515 pages. W. B. Saunders Company, Philadelphia and London.
- Infant Feeding.* By Clifford G. Grulee, A. M., M. D. Illustrated, second edition, thoroughly revised. 1914. 8°. 313 pages. W. B. Saunders Company, Philadelphia and London.
- Bedside Hematology: An Introduction to the Clinical Study of the So-called Blood Diseases and of Allied Disorders.* By Gordon R. Ward, M. D. (Lond.). 1914. 8°. 394 pages. W. B. Saunders Company, Philadelphia and London.
- Diseases of the Heart.* By John Cowan, D. Sc., M. D., F. R. F. P. S. With Chapters on the Electro-Cardiograph. By W. T. Ritchie, M. D., F. R. C. P., and the Ocular Manifestations in Arterio-Sclerosis. By Arthur J. Ballantyne, M. D., F. R. F. P. S. 1914. 8°. 438 pages. Lea & Febiger, Philadelphia and New York.
- Contribution to the Knowledge of Colloidal Nitrogen in Urine.* Thesis. By Pieter Johannes Louis de Bloeme. Translation from the Dutch. 1914. 8°. 86 pages. J. H. de Bussy, Amsterdam.
- Nucleic Acids, Their Chemical Properties and Physiological Conduct.* By Walter Jones, Ph. D. 1914. 8°. 118 pages. Longmans, Green & Co., London, New York, Bombay and Calcutta.
- Progressive Medicine.* A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Volume II. June, 1914. 8°. 460 pages. Lea & Febiger, Philadelphia and New York.
- Black's Medical Dictionary.* By John D. Comrie, M. A., B. Sc., M. D., F. R. C. P., Edin. Fifth edition, completing thirty thousand. Containing 431 illustrations in the text, etc., and 12 plates in color. 1914. 8°. 858 pages. The Macmillan Company, New York; Adam and Charles Black, London.
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A Text-Book of Pathology. By J. George Adami, M. A., M. D., F. R. S., and John McCrae, M. D., M. R. C. P. (Lond.). Second edition, revised and enlarged. Illustrated with 395 engravings and 13 colored plates. 1914. 8°. 878 pages. Lea & Febiger, Philadelphia and New York.

HELP FOR BELGIAN PROFESSORS AND OTHER REFUGEES AT OXFORD.

LADY OSLER'S APPEAL.

A letter received from Lady Osler speaks of the arrival in Oxford of refugees from Louvain University consisting of professors with their families and some alone, who had escaped from the burning town with only the clothes on their backs and barely enough money in their pockets to cross the Channel to Folkestone, and students from other parts of Belgium. The women and children were overcome with the horrors of the situation and the professors were stricken by the loss of their libraries, laboratories and the treasures of their ancient university. One professor escaped from Louvain with his wife, two babies and a manuscript which was said to be the only remnant of the famous collection in the Louvain Library.

Hospitality is being most generously offered by members of Oxford University, but at the moment the financial demands are enormous, and with reduced incomes it is difficult to meet all calls.

Lady Osler hopes to raise money to relieve the immediate wants of these stricken people and will be grateful for any sums, feeling sure of the universal sympathy felt.

Subscriptions can be sent to

MRS. THOMAS B. FUTCHER,
23 W. Franklin St.,
Baltimore, Md.

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UNIVERSITY OF ILLINOIS
3 JAN 1915

BULLETIN

OF

THE JOHNS HOPKINS HOSPITAL

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TWENTY-FIFTH ANNIVERSARY OF THE JOHNS HOPKINS HOSPITAL.
1889-1914.

PUBLIC EXERCISES.

During the year 1914 The Johns Hopkins Hospital completed the twenty-fifth year of its active existence.

To commemorate the event the trustees of The Johns Hopkins Hospital and of The Johns Hopkins University, all officers and former members of the hospital staff, all teachers, former members of the staff and graduates of the Training School for Nurses, and all teachers and former students of the medical department of the university were asked to be present at a general reunion to be held upon October 5, 6, 7 and 8, 1914. A large number responded to the invitation and were present from the United States and Canada.

The opening exercises were held at the Lyric at 3 o'clock on Monday, October 5. Henry D. Harlan, President of the Board of Trustees of The Johns Hopkins Hospital, as chairman, presented Rev. E. H. Griffin, D. D., LL. D., Dean of The Johns Hopkins University, who offered the following

PRAYER.

Almighty God, unto whom all hearts are open, all desires known, and from whom no secrets are hid, cleanse the thoughts of our hearts by the inspiration of Thy Holy Spirit, that we may perfectly love Thee, and worthily magnify Thy holy name.

We bring Thee, O Lord, devout and grateful thanks for Thy favor vouchsafed unto this institution, whose work of healing and mercy, during these many years, we this day commemorate. For the sympathy with human need, and the desire to alleviate human suffering, which prompted the great benefaction upon which this hospital has been established; for the munificence of those who, from time to time, have, by their gifts, enlarged its scope and augmented its resources; for the fidelity and wise counsel of those who, as trustees, have guarded its interests; for the self-forgetting devotion of those who have carried the heavy responsibilities of administration; for the high intelli-

gence, the varied attainments, the refined and disciplined skill, so freely placed at the service of the sick and the poor by its physicians and surgeons; for the patience and tenderness of nurses in the wards and at the bedsides: for all these expressions of thought and care and love and sacrifice, the sum of which cannot be numbered, we reverently and gratefully praise Thee, of whose only gift it cometh that Thy faithful people do unto Thee true and laudable service, by whose holy inspiration we think those things which are good, and by whose merciful guiding we perform the same. In all things well and worthily done we are the vehicles and instruments of Thy grace. "Not unto us, O Lord, not unto us, but unto Thy name be glory, for Thy mercy and for Thy truth's sake."

O Lord our heavenly Father, as Thou hast so abundantly blessed the work of these past years, we invoke Thy continued favor for the time to come. May the succession never fail of those who, in the love of God and of their fellow men, shall be ready to cooperate in the beneficent labors of this hospital: liberal benefactors who shall consecrate their wealth; men versed in affairs who shall contribute their experience and their foresight; profound investigators, moved by no lower motive than that they may give a true account of their gift of reason to the benefit and use of men; masters of the art, as well as of the science, of healing, commanding all resources of knowledge and all appliances of skill; Brethren of Pity, Sisters of Mercy, conveying through their ministries consoling gifts of patience, courage and hope. "Whoso hath the world's goods and beholdeth his brother in need, and shutteth up his compassion from him, how doth the love of God abide in him? May we not love in word, neither with the tongue, but in deed and in truth."

Almighty God, who hast directed that prayers, intercessions, and thanksgivings be made for all men, we beseech Thee with Thy favor to behold Thy servants, the President of the United States, the Governor of this state, the Mayor of this city, and

all others in authority; and in this time of world-wide calamity and distress, when the great peoples of the earth stand in arms against one another, we implore Thee, Ruler of the destinies of the nations, in whose hand are the hearts of kings, so to direct the movement of events, so to dispose human thoughts and purposes, that out of these cruel and direful sufferings and losses there may come a righteous and abiding peace. Have pity, O Lord, upon the wounded and dying, unbefriended upon fields of battle. Constrain compassionate hearts, in all lands, to send relief, and enable those for whom there is no help of man to put, in the hour of utmost need, their whole trust and confidence in Thee.

Our Father who art in heaven, hallowed be Thy name, Thy kingdom come, Thy will be done on earth as it is in heaven, give us this day our daily bread, and forgive us our trespasses, as we forgive those that trespass against us. And lead us not into temptation, but deliver us from evil, for Thine is the kingdom, the power and the glory, forever and ever. Amen.

Judge Harlan then spoke as follows:

REMARKS OF JUDGE HARLAN.

Twenty-five years have elapsed since The Johns Hopkins Hospital was opened, and it has seemed well to the board of trustees, its officers and medical staff to ask those who have been connected with carrying out the beneficent wishes and purposes of the great founder to return here and unite with us and our numerous friends in recalling and celebrating the accomplishments of this period.

We are highly gratified that so many have responded to our invitation, coming from far and near, and we welcome them one and all on this auspicious occasion. We welcome also many distinguished guests who have come to rejoice with us. We welcome the Mayor of Baltimore, the judges and other high officials whose presence dignifies the occasion. And we welcome all of our friends who have assembled in such goodly numbers to take part in our celebration.

There are many whose presence we miss. Some whose services were of inestimable value to The Johns Hopkins Hospital and Medical School are absent because they rest from their labors, but the memory of their works and deeds will be cherished and revered as long as the Hopkins foundations remain. Others there are who are kept away by imperious calls elsewhere. Many of these have sent their congratulations and good wishes. We regret their absence. We particularly regret the absence of Sir William Osler, to whom The Johns Hopkins Hospital owes so much, who had promised to attend and make one of the principal addresses of the occasion, but who has not found it possible to leave England by reason of new duties and obligations of the most important nature that have come to him as the result of the unexpected outbreak of the greatest war of all history.

There is one obvious duty of this hour. It is that we fail not to recall that Baltimore merchant who, finding himself possessed of a fortune, which his thrift and industry had pro-

duced, and believing that it had been given to him in trust for some great purpose, after anxious consideration resolved that it should be devoted to founding in this city, where his wealth was earned, a hospital and a university—in one of which the sick poor might be cared for and, if possible, healed; and in the other of which all seekers after knowledge and truth might find means and opportunity to gratify their highest aspirations. The record of twenty-five years attests the wisdom of his forethought and has shown the abundant fruits of his philanthropy. The story of these years is to be briefly told by others who are to speak, but let us at the outset, with one accord, renew our gratitude to Johns Hopkins, the founder, and remember him whose name must be written large on the pages of any book in which is recorded the names of those who have served their fellow men.

Next to Johns Hopkins we should recall those early trustees to whom Johns Hopkins gave, not a hospital, not even a plan for a hospital, but money and property valued at \$3,228,404.84 and a few simple directions; and to whom he entrusted the task of building, equipping, organizing and operating a hospital. They were men of broad vision, they appreciated the obligations laid upon them, they saw and seized upon the opportunity which was at hand, and with the help of wise advisers they created and organized a hospital which has become known the world over, and which, while its object has not been to treat a maximum number of patients, but to treat as many patients as its resources would allow with a maximum amount of care and skill, has in twenty-five years received into its wards 95,689 sufferers, and to its out-patient department 1,561,239 visits have been paid, which has given to the world in connection with the medical school of the university, of which the founder desired it should be a part, men and women who in their several professions, as physicians, surgeons or nurses, have made notable contributions to knowledge, to science and to education.

The trustees of to-day are endeavoring to carry out the purposes of the founder as they have been interpreted and handed on to them.

When the hospital was opened, its productive endowment was \$3,286,962.54; and the property under the care of the trustees, including the endowment and hospital buildings, amounted to \$5,355,313.50. The productive endowment has increased more than half a million, and the property under the care of the trustees now amounts to \$7,838,442.32, not including The Harriet Lane Home and The Brady Urological Institute. This increase is due in part to an appreciation in the value of investments, some of which were made by the founder himself, but it is more largely due to a number of generous gifts of money or buildings and some splendid benefactions. The names of the benefactors will be appropriately mentioned by others, but the trustees are deeply sensible of the approval thus accorded to the work of the medical staff and of the confidence that has been manifested in the officers and management. The chief function of the trustees is to conserve the endowment, to make it productive, to increase it if possible, to apply it wisely, with the help and advice of the medical board, to the hospital's needs and opportunities.

Large as is the property under our care (though it is inadequate to enable us to advance into fields of usefulness that are constantly opening), the greatest endowment which The Hopkins has is the spirit of loyalty and service that pervades its staff and its employees. It is their devotion, their zeal, their cooperation, their skill, their learning and their ability which have brought it into prominence and made it useful. We acknowledge this with the greatest sense of appreciation.

Looking back upon a fruitful past, we turn our faces toward the coming years with high hopes and the confident belief that under Divine favor a future of greater usefulness is yet in store for The Johns Hopkins Hospital.

President F. J. Goodnow, of The Johns Hopkins University, was then introduced and spoke as follows:

PRESIDENT GOODNOW'S ADDRESS.

The occasion which we celebrate to-day is one which cannot fail to arouse feelings of satisfaction and pride among the friends of The Johns Hopkins Hospital and The Johns Hopkins University. To-day marks the accomplishments of twenty-five years of arduous effort. This occasion is a public attestation that the beneficent intentions of him to whom the hospital and medical school owe their existence have been carried out. It is more than that. It is proof that the plans made so many years ago have approved themselves both to other benefactors and to the world at large. For the generous support which has been received indicates in a most certain way that no serious mistake has as yet been made by those in charge. May we not hope that the support will continue in the future? With it, the hospital and the medical school will be able to widen their sphere of useful effort. Without it, it can hardly be expected that past achievements will be surpassed.

To the sagacity and foresight of those who, for years before the opening of the hospital we commemorate to-day, planned the present undertaking, are due the completeness and convenience of its buildings and appointments. To those who have put into execution the plans then adopted are to be attributed the excellence of the organization and the high character of the personnel which from the beginning have been the aim sought. To the able and indefatigable staff which it has been the good fortune of the hospital and the medical school to have from the beginning of their history is to be credited the success which has always been associated with Johns Hopkins medical work.

The influence and reputation of the hospital and the medical school have become international. But they have become so without lessening in any way the benefits it was the intention of the founder of this great enterprise to confer upon the community in which he had lived his life.

But while this occasion is thus of great interest to all friends of The Johns Hopkins Hospital and University as well as to all engaged in medical instruction, it has a peculiar significance to me.

As some of you undoubtedly know, the last year or more of my life has been spent in the East. In China, the particular

part of the East in which it was my lot to reside, there is, except where Western influence has been almost controlling, no such thing as a hospital. Nor has there been any such thing as a medical school.

The absence of hospitals has been due to the lack of the cooperative spirit among the people as well as to the general application in the country of the law of the survival of the fittest. *Sauve qui peut* is almost the only rule of conduct which is really understood and acted upon by the Chinese people.

The absence of medical schools is to be attributed to the fact that a learned medical profession does not exist. There are, it is true, physicians. But they practice what is in the nature of a trade rather than a profession. Their knowledge is based upon their own rather limited experience supplemented by what they may have learned from their predecessors, who are often their ancestors or relatives. Little if any attempt is made by them to impart to others the knowledge which they possess. On the contrary their own particular trade secrets are often jealously concealed. In these circumstances the development of a science of medicine is naturally impossible, and the existence of medical schools is not to be expected.

I have come thus from a country where the conditions are such as I have described, to a city in which the hospital and the medical school are supremely important features in the community life, where the twenty-fifth anniversary of the foundation of The Johns Hopkins Hospital is made the occasion of a memorable celebration such as that in which we are now participating.

I can therefore hardly fail to contrast the civilization which I have left with that in which it is my good fortune to work. At the present moment, it is true, one can with difficulty banish the thought that European civilization is being put to a test to which it has not for many years been compelled to submit, a test which many of us hoped was not in the future to be required of it. Many persons are perhaps inclined to counsels of despair. Some even may consider that we are relapsing into barbarism and that our civilization has become bankrupt.

It is well, however, for us to remember in these sad and somber days that the alleviation of suffering and the cure and prevention of disease are more distinctive characteristics of European and American life than the wars which bulk so large at present in the public vision. War has always been a weakness of the human race. Peace has never for long been characteristic of any of the civilizations which man has developed. But the hospital and the medical school, to further whose work we are assembled here to-day, are really the most marked incidents of modern European life. The alleviation of suffering for which the hospital stands is an evidence of the high degree to which social cooperation has been developed. The attempt to prevent and cure disease, which is the work of the medical school, is an instance of the application of the scientific method to the conduct of the ordinary affairs of life. This capacity for social cooperation, this attempt to regulate our lives by the dictates of science, are to my mind the peculiar attributes of Western civilization. Living as we do, we are apt

to take them for granted. It is only when we leave the environment in which we are now living that we see how remarkable a development they are in the history of man.

This occasion has also peculiar significance for me because it is the first time that I have been called upon to endeavor to take in public the place which was so effectively filled by my illustrious predecessors, President Gilman and President Remsen. President Gilman's contribution to the cause of higher education in the United States is too well known to you even to require mention. I fancy, however, that the work which he did for the hospital is not so generally known. Not only was he the first president of The Johns Hopkins University and one of the leading university presidents of his day; his also is in large measure the credit for the organization of the hospital. His work in connection with that institution was so important and so comprehensive that he may almost be said to have been its first superintendent.

It was due to his wisdom and tact, and to that of his immediate successor, and to the cordial cooperation which has always existed between the boards of trustees of the hospital and the university, that the relations between these institutions have been such as they are. I have been told that these relations are indefinable; that they have not been reduced to writing where they may be subjected to the cold criticism of the curious inquirer; that on the contrary they are enshrined in the warm hearts of those who love the work they are engaged in doing. Such a spirit as now exists is in no small measure responsible for the success which has thus far attended the efforts of those in charge of these two great undertakings.

I feel certain that that spirit will continue to animate those who in the future will be called on to carry on this work, that the hospital and the medical school may envisage the days to come with confidence, and that their influence will increase and their reputation will surpass even that which they now enjoy.

Dr. W. S. Thayer was introduced and read the following communication from Sir William Osler:

COMMUNICATION FROM DR. OSLER.

"LOOKING BACK."

That all of us in control of departments at the opening, should have been spared to see this twenty-fifth anniversary of the hospital, is a piece of singular good fortune. It is a small matter that I am not with you.

Where the greater malady is fixed
The lesser is scarce felt

expresses my feeling in the present crisis. You all know how I should have enjoyed the reunion with so many so dear to me by the strongest ties that bind man to man—the same ideals in life, the same pride in a splendid heritage, and that sense of close comradeship enjoyed by men who have initiated a great work and have survived to see it successful beyond their wildest dreams.

The Johns Hopkins Foundations were only grafts on the educational tree, grafts that would have withered had they not partaken of the root and fatness—to use a Biblical phrase—of its natural branches. Great biologists before Martin, great physicists before Rowland, great chemists before Remsen, great Grecians before Gildersleeve, had had their day in America. It was not the men, though success could not have come without them, so much as the method, the organization, and a collective new outlook on old problems. They were gathered here from all parts to do one thing, to show that the primary function of a university was to contribute to the general sum of human knowledge. On the way they could teach, and they had to teach what the fathers had taught, but this was only as a means to a definite end—viz., in science and in arts to widen man's outlook so as to strengthen his dominion over the forces of nature. Individuals here and there for generations had had in this country these ideals, but never before a *studium generale*, a whole body of men gathered in one place to form a university. That part of the university which, with the hospital, forms the medical school has only had twenty-five years of existence, not a generation, a mere fraction of time in the long history of the growth of science, so that it seems presumptuous to claim any powerful influence on the profession at large. The feeling, however, is strong, too strong to be passed over, that the year 1889 did mean something in the history of medicine in this country. One thing certainly it meant, as originally designed by that great leader Daniel C. Gilman, that the ideals of the men on this side of Jones Falls were to be the same as those of the men in the laboratories of North Howard Street, that a type of medical school was to be created new to this country, in which teacher and student alike should be in the fighting line. That is lesson number one of our first quarter-century, judged by which we stand or fall. And lesson number two was the demonstration that the student of medicine has his place in the hospital as part of its machinery just as much as he has in the anatomical laboratory, and that to combine successfully in his education practice with science, the academic freedom of the university must be transplanted to the hospital. Again it was not men, but a method, initiated in Holland, developed in Edinburgh, matured in London, and long struggled for here, but never attained until The Johns Hopkins Medical School was started.

And binding us all together there came as a sweet influence the spirit of the place; whence we knew not, but teacher and taught alike felt the presence and subtle domination. Comradeship, sympathy one with another, devotion to work, were its fruits, and its guidance drove from each heart hatred and malice and all uncharitableness.

Looking back, these are my impressions of the work of The Johns Hopkins Hospital.

But I must touch a personal note, and pay a tribute of affection to the men who helped to make my special clinic. In those early days of happy memories Booker and Harry Thomas in the dispensary sowed the good seed which has thriven so wonderfully in great new departments. Lafleur, Reese, Toulmin, Scott, Thayer, Hewetson, Simon, Hoch, Frank Smith

and Barker helped to organize in those plastic first years our methods of work. No one feature contributed more to the development of the hospital than the presence in each department of a group of senior assistants. I look with a justifiable pride at the work of these men. In succession during my term, Lafleur, Thayer, Fitcher, McCrae, Emerson controlled the work, and my indebtedness to them cannot be expressed in words. Always loyal and considerate, no chief ever had more devoted helpers. And we were singularly fortunate in our assistants, senior and junior. The list is too long to tell over. Many came from outside schools, but the spirit of the place soon came upon them. Scattered far and wide now in important posts, they know how my heart follows them in their work, and how proud I am of their success. To have more than thirty of one's "boys" actively engaged in teaching is to draw a big prize in the lottery of life with which for solid satisfaction there is nothing to compare.

But shadows flit across the picture—dark memories of the men whose leaves perished in the green. Jack Hewetson we all loved, I as a son, Thayer, Barker and Frank Smith as a brother. There was a light in his blue-gray eyes that kindled affection in all who knew him. Meredith Reese, the first to go, stricken also with tuberculosis, left us with scarred hearts. Livingood, whose mental outfit promised a career of special brilliancy, met a tragic death in the Bourgogne. Lazear, who went from the clinical laboratory to join Walter Reed, died a martyr's death in Cuba. Oppenheimer and Ochsner, men of great merit, died on duty in the hospital. John Bruce MacCallum, in intellect "the bright particular" among our students, lived long enough to snatch something from dull oblivion. Al. Scott, whom we all loved dearly, had a successful career in Philadelphia before the call came. And only recently we have to mourn two of our best: Rupert Norton was one of the finer spirits, only touched to fine issues in a suitable environment, and that he found here in the latter years of his all too brief life. Otto Ramsay, who came to our clinic first, became one of the most successful teachers and practitioners in New England.

The Johns Hopkins Hospital illustrates the growth of an idea, represented by the founder, and the intelligent cooperation of different units. The foundation-stones were laid by the adviser, John S. Billings, by Francis T. King, the president, and by the board of trustees. Under the wise guidance, at first of President Gilman, then for long years of Dr. Hurd, the organization grew apace, and the hospital was made a fit habitation for patients by the work of Miss Isabel Hampton, Miss Rachael Bonner, and Mr. Emery. The medical staff has used the facilities thus afforded for the benefit of the public in curing the sick, in studying the nature of disease, and in training men to do the same, with what measure of success we must leave to the judgment of posterity. To me at any rate there remains a precious memory of the years I spent at Baltimore, and an enduring pride that I should have been associated with the work of this hospital.

(Signed) WILLIAM OSLER.

Dr. Henry M. Hurd, the former superintendent of the hospital, then gave the following address:

DR. HURD'S ADDRESS.

When I was informed that I should have the honor and privilege of addressing you upon this anniversary, I was given to understand that my brief remarks were to relate to the history of the hospital. In view of the additional fact that by the same appointment it was made a part of my duty to prepare a detailed account of the growth and development of The Johns Hopkins Hospital during the past twenty-five years for publication as one of the volumes of the Hospital Reports, I shall content myself upon this occasion with presenting such details as may be of general, not to say popular, interest.

The site of The Johns Hopkins Hospital had been dedicated to the uses of a hospital since 1797, when, in consequence of epidemics of yellow fever, introduced into Baltimore by the West India trade, public attention had been directed to the necessity of provision for the friendless sick. Little at first was done beyond the purchase of the site by the state and the erection, partly by the state and partly by private enterprise, of a building modeled apparently upon that of the Pennsylvania Hospital, with an administrative center building and two wings upon the east and west sides of it. The whole enterprise languished and finally fell by lease into the hands of two eminent physicians of Baltimore who conducted it in turn as a Seaman's Hospital, a hospital for the insane and a public hospital for medical teaching. After the lapse of more than thirty years the State of Maryland reasserted its right to the property, which originally had been purchased by it, and established an institution for the insane exclusively. Under contract it also provided for the insane of the District of Columbia for many years. The Maryland Hospital for the Insane, as it was termed, was conducted by a board of visitors representing Baltimore and the different counties of Maryland, and many well-known philanthropic men served the state in this capacity without compensation. Among others were Dr. Richard Sprigg Steuart, Johns Hopkins, Francis T. King, Judge George William Brown, Judge George W. Dobbin and Enoch Pratt, names well-known to all. There is every reason to believe that Johns Hopkins, while serving upon this board of visitors, early gained an interest in the sick and suffering and learned their needs. Judge Brown, Francis T. King and Judge Dobbin all spoke to me of the desire expressed by him to continue the work of relieving human suffering upon the spot which had been consecrated by seventy years of service, after the Maryland Hospital had been removed to Catonsville.

The founder of The Johns Hopkins University and The Johns Hopkins Hospital died upon December 24, 1873, before either institution had been organized or put into operation. For several years Mr. Hopkins had given much thought to their establishment and had not only procured acts of incorporation for the twin foundations, but had also appointed boards of trustees to manage them when they should be set in operation. The hospital, the site of which he had already

purchased, had evidently been in his thoughts for a long time, to judge from the interesting reminiscences of his relatives and associates upon the governing board of the old Maryland Hospital for the Insane, handed down by tradition. It is reasonable to infer that like other philanthropists he talked with many persons and received advice from many quarters, and that no one person can claim the sole credit for the suggestion. Mr. Hopkins, as Francis T. King so well said in an address at the opening of the hospital in 1889, felt that his wealth had come to him in trust only for the benefit of mankind and that he had the responsibility of a good steward to make the best use of it. He consulted with Dr. Parrish, of Philadelphia, with John W. Garrett, with Charles J. M. Gwinn, with Judges Brown and Dobbin, with Dr. Fonerden, with Dr. Alan P. Smith, with Francis T. King and with his relatives and friends. The need of better hospital construction was in the air largely because of the impetus received during the late Civil War, which witnessed the first organized effort to treat the sick and wounded in this country upon a large scale in buildings erected with due precautions as to ventilation, the segregation of patients and sanitary requirements. In a sagacious and unique letter addressed a few months before his death to the board of trustees of the future hospital, he gave specific directions as to the character of the buildings and the arrangement of the grounds; directed the establishment of a training school for nurses; provided "for the reception of a limited number of patients who are able to make compensation for their room and attention"; spoke of the desirability of a convalescent hospital to hasten the recovery of the sick and to provide "room in the main hospital buildings for other sick persons requiring immediate medical or surgical treatment"; made it a special duty to "secure for the hospital surgeons and physicians of the highest character and greatest skill"; and above all, enjoined them to bear constantly in mind the "wish and purpose that it should form a part of the medical school of that university for which I have made ample provision in my will."

In 1867 Mr. Hopkins had procured an act of incorporation from the Maryland legislature and had named as trustees of the hospital twelve friends and business associates. As far as can be determined by the records, many of the original incorporators took little active part in the final organization of the new hospital, and several in fact died before the property which was set apart by the will of the founder for its support had passed into their control. Little effective work seems to have been attempted by any one until the year 1874, when the dilapidated hospital buildings which had been on the site for nearly sixty years were torn down. The guiding spirit in the earlier days of the hospital was unquestionably Francis T. King, the first president of the board, to whom reference has already been made. He called into his service five hospital experts—Joseph Jones, of New Orleans; John S. Billings, of the U. S. Army Medical Corps; Casper Morris, of Philadelphia; Norton Folsom, of Boston; and Stephen Smith, of New York, who each prepared plans for the future hospital and also drew up schemes for its organization, equipment and

general management, all of which were published and widely circulated. Mr. King had an invincible optimism, great breadth of view and an abiding enthusiasm which rendered him invaluable at this formative stage of the enterprise. He early recognized the ability of Dr. John S. Billings and it was largely through his influence that the preparation of plans and the responsibility for their translation into bricks and mortar were committed to Dr. Billings. The indebtedness of the enterprise to the latter can never be overestimated. He grasped the intentions of the founder and possessed the vision to see the new hospital before any portion of it was constructed. He was also able to impress his views upon all who came in contact with him. He was an able surgeon, a sanitarian, a bibliographer and a scholar with large experience and expert knowledge of every branch of medical science. He knew what ought to be done and what should be avoided in all attempts to promote medical education and medical research. The trustees of the hospital, intelligent, high-minded men, desirous of the best results although unfamiliar with medical problems, gave him their confidence and support and were thoroughly cooperative in all his plans. Since 1867 thirty-eight persons have held the office of trustee of the hospital. Of these, twenty-four have died in office, three have resigned—one in order to become treasurer, and two because of ill-health. The remaining eleven persons constitute the present board. The services of Francis White, Judge Brown, Judge Dobbin, George W. Corner, William T. Dixon, the second president, who held office for eleven years, John E. Hurst, John A. Whitridge, Joseph P. Elliott, C. F. Mayer, Skipwith Wilmer, R. M. Venable, Charles J. M. Gwinn and C. Morton Stewart were most valuable to the hospital and are worthy of special mention here.

If the plan of organization and the development of The Johns Hopkins University had been less revolutionary and its immediate success less phenomenal, it is not improbable that the trustees might have hesitated to plan a hospital on such an extensive and expensive scale to promote the teaching of medicine. The success of the university in teaching the fundamental branches of chemistry, physiology, biology and pathology in systematic courses had opened a new era of scientific inquiry in the United States. Students were flocking to H. Newell Martin to receive laboratory training in biology and physiology, to Welch for pathology and to Remsen for chemistry. They became unwilling to cease their scientific work when they entered upon the study of medicine, which at that time seemed more generally pursued in the lecture room and amphitheatre than in the hospital ward at the bedside in actual contact with disease, or in the laboratory in the study of diseased processes. Important changes in methods of medical study and investigation were impending, and all recognized the desirability of the construction of a hospital which would embody the newer conceptions of medical progress. Acland, Huxley, Billings and others, in addresses before Baltimore audiences, had impressed upon all thinking men who heard them the need of grounding medical education upon the firmer basis of knowledge acquired in the laboratory by the student

himself. Many of these ideas also had already been elaborated in the volume of essays before mentioned and had borne fruit.

The plans which represented these newer conceptions were painstakingly considered by the trustees and finally placed in the hands of Dr. Billings to be perfected. As the resulting revision did not please him, he took them to Europe to consult many experts and to secure criticisms and suggestions. After an absence of several months he returned to present a set of plans which was ultimately adopted. They were modified, however, in important particulars, during the course of construction, which extended over a period of twelve years, being begun in 1877 and completed in 1889. The buildings were thoroughly well-built, almost massively built, as has been satisfactorily shown whenever it became necessary to cut through any walls or to remove any portion of them to make changes. Experienced builders of the present day have declared them to be needlessly well-built, but this defect seems pardonable and possibly admirable even in these days of concrete and steel not yet tested by time and the elements.

Francis T. King was also unquestionably the moving spirit in the erection of buildings. He persuaded Mr. Hopkins to consent to the enlargement of the original site by his quiet persistence and vision of the possibilities of a frontage upon North Broadway, facing and overlooking the city and the hills to the west, affording a glimpse of the harbor, instead of one upon a narrow, unimportant street with a northern outlook. Dr. Billings was selected as permanent medical adviser to the trustees; and competent architects in Baltimore and Boston were chosen to make elevations and working plans according to ground plans made by Billings. The work of erecting the buildings was not placed in the hands of contractors, but was done by day's work under the constant supervision of able and honest superintendents of construction. Francis T. King also became warmly interested in the Isolating Ward Building, which owes its present shape to his suggestion, and was especially insistent that the building designed for the use of nurses should be a model of excellence and of sanitary perfection. He had received many suggestions as to the proper housing of a training school for nurses in a prolonged interview with Florence Nightingale in London, and urged their incorporation in this building.

It seems appropriate to refer to the criticisms which were patiently endured by the trustees because the hospital was so long under construction. As the buildings were to be built no faster than the income accrued, it was not practicable to hurry the work without encroaching upon the principal and jeopardizing the future. The criticisms were honestly made and dictated by good motives, but they failed to take into account the extent of the educational problem involved. A mistaken financial policy at this time would have clouded the whole future of the institution. All honor to the men whose watchful waiting permitted the attainment of the present success!

When the buildings were ready for occupation, President Gilman, of The Johns Hopkins University, was asked to direct the organization and opening of the hospital. The excellent

character of the work which he accomplished in this capacity has been referred to at length in some remarks which I made upon another occasion. His services were most valuable and gave a character to the work of the institution which it has ever since retained.

He also assisted in the selection and recommendation for appointment of the chief medical officers, of the matron, of the purveyor, the superintendent of nurses and the superintendent of the hospital, and thus retained for a long time a personal touch with the administration of the institution. The appointments to the staff in order of seniority were: Drs. Welch, Osler, Halsted and Kelly. There were many other excellent candidates for appointment, and some disappointments, of necessity, but time has healed the wounds and all agree that great wisdom was shown and great benefits followed the combined counsel of Gilman, Billings, Welch, Remsen, Osler, who constituted the first advisory board, and others. At any rate the hospital staff proved to be harmonious and a unit to utilize to the utmost the facilities of the hospital for the advancement of medical science. It is difficult for me to think of those early days without deep emotion. The majority of the members of the staff were young and full of energy and hope. They toiled without remission and were eager students. Medicine had awakened from the lethargy of almost a century, and under the stimulus of the discoveries of Koch and Pasteur was fast becoming transformed into a living, breathing science. Surgery, under the lead of Lord Lister, had assumed a definiteness and precision which permitted it to explore with safety and success new regions of the human body and to cure many hitherto hopeless conditions. A definite bacillus had been discovered as an organism growing in the human body and proven to be the cause of tuberculosis and capable of transmitting the fatal disease to other persons. It was no longer necessary to fall back upon the theory of the inevitable transmission of the disease from ancestors and immediate relatives or to deplore its tendency to develop upon clay soils or to look upon it as the inevitable termination of almost every wasting disease. Malarial disease was known to be no longer due to miasma mysteriously generated in marshy ground or to vapors of unknown origin, but rather to a specific organism introduced into the blood from without and capable of demonstration. These and a host of other similar discoveries rendered every one eager to confirm recent discoveries and to add to their number. The result was the gathering of a band of young men under competent leadership who attacked new problems and worked without haste and without rest. They studied disease at the bedside, in the clinical laboratory and in the pathological institute.

It was, in my judgment, most fortunate for the development of the future medical school that the hospital was first opened and had become thoroughly established in its clinical methods of study prior to the opening of the school. The methods inaugurated by The Johns Hopkins Hospital constituted a new era in this country in the teaching of medicine, surgery, gynecology, obstetrics and pathology; and in clinical laboratory methods.

Dr. Halsted established foundation principles of surgery; Dr. Osler inaugurated thorough methods of clinical study of internal diseases; Dr. Kelly elaborated methods of diagnosis and operative technique; Dr. Williams revolutionized the practice of obstetrics; while, in the Pathological Institute established in 1886, the first department of the hospital before there was a hospital, Dr. Welch sat in final and authoritative judgment upon all branches of the work.

I well remember the comprehensive plans of Dr. Osler for the establishment of the first clinical laboratory in a single, small basement room and its subsequent development through the broad-minded and sagacious liberality of two women of Baltimore, whose names I am not to mention, into the present clinical laboratory of The Johns Hopkins Medical School.

The establishment and organization of the Training School for Nurses were equally profitable to scientific medicine. The hospital was opened in May, and during the interval between May, 1889, and October of the same year the work of nursing had been committed to graduates from different schools, many of which possessed varying degrees of preliminary requirements for their pupils. Three had been English-trained nurses and two of them army nurses in Egypt. The remainder were representatives of training schools in this country. They were all faithful, diligent and competent, but the lack of a superintendent and the absence of uniform standards of nursing work left something to be desired. Hence the coming of Isabel Adams Hampton at the time of the formal opening of the school in October, 1889, inaugurated a marked advance in nursing methods. Miss Hampton had received a broad training in this country, which had been supplemented by unusual study in Europe, and had later acquired a personal knowledge of educational and administrative work through her successful supervision of the Illinois Training School in Chicago. She had little sympathy with the conception that the nurse shall be a mere automaton, competent only to do what she had been told to do by some other person and destitute of all initiative; on the contrary, she believed that her work required an adequate training of mind, heart and body so that every good nurse might know how to accomplish the best results and to meet new emergencies as they arose. Hence she advocated and established a thorough course of study, with shorter hours of work and provision of time for study. She made the service more attractive to women of education and refinement and sought to obtain those who had high ideals of service and a good preliminary education to enter upon study. She endeavored in short to make nursing a profession and not a mere method of getting a living. The success which crowned her efforts is well shown by the standing of the school from the start and the influence it has had, not only on the nursing standards of Baltimore, but also upon those of the whole country.

The development of the publications of the hospital, which have also had a marked influence upon medical science, is due largely to Dr. Osler. He first suggested the preparation of the Reports and, undeterred by obstacles which deferred the publication of Volume 1 for seven years, he set at work upon

Volume 2 and wrote or inspired much of it. Without his industry, energy, fertility and literary facility, I fear that the formidable series of volumes would not have extended beyond Volume 2; but his example was irresistible and the series has gone on until seventeen volumes of valuable monographs have appeared. He also suggested the establishment of the Hospital Bulletin, now in its twenty-fifth volume, which has done so much to make the hospital known throughout the medical world. This journal was designed originally to follow the lines of The Johns Hopkins University Circular, which contained programmes of courses, news items, announcements of lectures and brief papers or announcements of original observations to be published later more in detail in more ponderous journals. To avoid complications with the Circular, it was named the Bulletin at the suggestion of Judge Dobbin, and began its modest career in December, 1889. From the start the Bulletin proved a great success, and has filled an increasingly useful place in the history of the hospital. It has furnished a place for the speedy publication of papers and researches on the part of members of the hospital staff. The fact that such an opportunity has existed for publication has unquestionably stimulated production and has improved the quality of our medical literature. It has contained original articles, reports of societies, notes and reviews of books and, above all, illustrations of medical papers which have done much to revolutionize the former methods of medical illustration. The credit of the latter belongs to Dr. Kelly, who conceived the importance of vivid and correct representations of medical and surgical conditions and sought to realize his ideals at large personal expense; and to Max Broedel, who possessed the mind of a scientist and the hand of an artist to portray these conditions to others. No medical illustrations have equalled them in scientific accuracy or artistic beauty, and no persons have been more instrumental in developing and perfecting methods of such illustration.

The staff of the hospital has also been active in the preparation of papers embodying the results of researches and also of many monographs and text-books. The number of such publications is too great to permit any more than this passing reference.

Shortly after the opening of the hospital and primarily in consequence of the insistence of President Gilman, who had the matter deeply at heart, courses were established for physicians in clinical and laboratory branches which served an excellent purpose until the founding of the medical school in 1893. When we remember that such men as A. C. Abbott, Walter Reed, Simon Flexner, G. H. F. Nuttall, J. H. Wright, Jesse W. Lazear, Frank R. Smith, George Blumer, W. W. Russell, Lewellys F. Barker, W. S. Thayer, J. G. Clark, T. S. Cullen, H. H. Young and others came to Baltimore because of these courses, we can appreciate how much they benefited the coming medical school by furnishing inspiring teachers and stimulating research workers. As the men who were engaged in teaching them are still with us, it is not proper that I should refer more in detail to their work as teachers. Much could be said which cannot with propriety be said now.

To the initiative of Dr. Osler we owe wholly the establishment of the distinctive hospital medical organizations. Upon October 6, 1889, he gathered the attending and resident staff of the hospital and dispensary together in the library and organized the Hospital Medical Society, which has now had an active existence of just twenty-five years. It began its career without any written constitution and has continued it without any organization. A president and secretary are chosen each year, and the traditions of the society seem to be the only fixed rules of government. Many eminent men from this country and abroad have appeared before it, and most of the most important contributions of the hospital to medical or surgical practice or progress have been announced first at its meetings. The older men, like Osler, Welch, Kelly, Halsted, Williams, Robb, Barker, Thayer, Finney, Clark, Bloodgood, Cushing, Walker, Thomas, Cullen, Russell, Young, Theobald, Randolph, Gilchrist, Lord, Mackenzie and many others, have shown a warm interest in it, and it still shows an amazing vitality.

The Hospital Historical Club was also organized through the active agency of Prof. Osler upon November 10, 1890, and has ever since had regular meetings. Dr. Welch gave at its first meeting a talk on the "History of Medicine"; Dr. Osler showed Dr. John Morgan's "Discourse on the Institution of Medical Schools," a very profitable discourse to be read to-day, and Dr. Kelly showed many rare medical books. The papers and discussions which have been presented before this club have had an important influence upon the study of the history of medicine in this country. The publication of many of the papers in the Bulletin has tended also to increase the spirit of historical research and has been of material assistance in rescuing many important medical happenings from oblivion.

A third society, also due to the clear vision and the wonderful organizing ability of Prof. Osler, was the "Laennec Society for the Study of Tuberculosis." This has accomplished a remarkable work in promoting the study of tuberculosis and has done much good.

There is no more gratifying chapter in the history of the hospital than the remarkable list of benefactions commencing with the legacy of the sum of \$1000 from the estate of the late Arunah S. Abell in 1889 down to the magnificent gifts of John D. Rockefeller, Henry Phipps, William H. Grafflin, Helen Wilmer, Charles L. Marburg, James Buchanan Brady and many others, aggregating more than two millions of dollars. Without them the work of the hospital would have been sadly curtailed, and after the great fire of 1904, in fact, it must have closed its doors temporarily for lack of funds. These gifts have often come "without observation," unsolicited and unexpected, but none the less have they been most timely. The needs of a constantly growing hospital are increasingly important. Thanks to a generous public, these needs have been met up to this time.

Of those who have been connected with the resident staff during the past quarter of a century, twenty-one persons—Brockway, Ramsay, Reese, Scott, Hewetson, Norton, Lazear, Reuling, Livingood, Huger, Oppenheimer, Stewart, Lanier, Bush, Edwards, Swan, Davis, Whitridge, Bettman, Ochsner

and Watson—have passed away. Thirteen were medical officers, four surgical, three gynecological and one obstetrical. The large number of medical men as compared with those in other departments points to the greater hazard of infection from tuberculosis, typhoid fever and acute epidemics in the medical than in the other services.

Whatever their service, however, they were zealous, earnest, painstaking and loyal men and their death is a loss to the profession of medicine. We rejoice in their efficiency; we remember their companionship; and we mourn their untimely deaths. Peace to their ashes! Their memory will always be cherished by those who knew their worth.

Prof. Adelaide Nutting, of Columbia University, a former superintendent of nurses and principal of the Training School, was then introduced.

ADDRESS OF PROFESSOR NUTTING.

THE WORK OF THE JOHNS HOPKINS SCHOOL FOR NURSES.

The Training School for Nurses of The Johns Hopkins Hospital was fortunate alike in the period in which it arose, in the city in which it was established, in the institution of which it formed a part, and in those who created and shaped its policy and directed its early growth and development. When this school was opened in the year 1889, the young profession of nursing was just beginning to awaken public interest.

The first sharp impetus had been given in the military hospitals of the Crimea, where, in the middle of the nineteenth century, Florence Nightingale made her astounding demonstration of the place and power of nursing in the reduction of mortality. Following closely upon this came the foundation by her of a school of nursing on scientific lines in a great and famous London hospital, and the rapid extension of her system of training into hospitals generally throughout the United Kingdom. The reforms in them which were initiated through her teachings are matters of history. They demonstrated again with unmistakable clearness the vital importance of nursing in the conduct of hospitals, and of medical and surgical practice. Some years later, in 1873, this system of training was brought over to America and a modern school of nursing was introduced into Bellevue Hospital in New York City. Its effect upon that venerable institution, which had long been the plaything of politicians and the despair of the charitable public, was as salutary and as striking as it had been in English hospitals. The place was completely revolutionized, and so eventually were the other hospitals which one by one adopted the new system. Law, order and decency were established, a sanitary régime was inaugurated, the mortality rate was brought down, and the confidence and esteem of the public were brought up. Medical men realized the value of the new ally which stood beside them at the bedside of the sick; the enlightened public was beginning to comprehend that a whole new situation in life had been shaped by the hands, the brains and the spirit of this body of women, who had in a few years wrought in hospitals an almost inconceivable transformation. Temptation to dwell on the devotion and the heroism of the

women who did that pioneer work in the hospitals of this country always assails me. I must resist it, but not without urging a study of those stirring pages of history which tell of their labors. Suffice it here to say that many able and educated and gifted women of exalted purpose had been drawn into the work; the highest ideals of service and self-sacrifice had been established; noble traditions of heroism had been created.

The glow of this first enthusiasm was as yet undimmed when The Johns Hopkins Hospital Training School opened its doors. Not only was it to lead women into a new and absorbing field of work, but at this time, it should be remembered, there were hardly any other fields of work open to them. Teaching was practically the only profession in which women were occupied in any appreciable numbers. The whole movement for the education of women was indeed in its early years, and some of the colleges of which we are now so justly proud were then just beginning to make their influence felt. Bryn Mawr was in its infancy. Barnard was just being founded, Radcliffe was as yet a dream. The time was a favorable one for the further development of this new work for women which was seen to be rooted in the vital necessities of life, and which had already made so strong an appeal.

The city of Baltimore, with its old-world tranquillity, its scholarly atmosphere, its far-famed hospitality to the stranger and to some of his ideas, had many unique institutions, educational, artistic and philanthropic, but among them there had not as yet appeared a training school for nurses. The field in this city for this new branch of women's education was wide and untouched; the place and the time were propitious. And further, this school was established in connection with a great new hospital, which had become famous in a sense, even before its doors were opened. To its planning many years of special study and arduous labor had been devoted, and it stood as an embodiment of the best thought and skill of the time in architectural form and structure, in internal arrangement, in hygienic provisions. As a part of the noble university which had become pre-eminent throughout the intellectual world, it was to be a center for advanced scientific teaching and for sound methods of work. Moreover, the training school was not to be a merely necessary factor in hospital administration, but was an institution as definitely provided for by the will of the founder as was the medical school. His directions read: "I desire you to establish," not "in," but "in connection with" the hospital a "Training School for Nurses." The school was, therefore, to stand on a strong foundation.

The nursing world should feel a peculiar sense of gratitude to that first board of trustees for finding and placing at the head of the school so remarkable a woman as Isabel Adams Hampton. Their instincts were unerring. Miss Hampton brought to her unusual opportunity an unusual breadth of capacity. Educated for teaching, but with leanings towards medicine, gifted with exceptional powers of leadership, she was also an organizer of large and far-seeing vision, an administrator of sound judgment and practical ability, strong in conviction, courageous, firm and determined in action. She was richly endowed mentally and physically, overflowing with

ardent and vigorous life, full of warm and generous impulses and radiant with endearing qualities. She cherished the most exalted ideals of nursing and of its future possibilities.

At the very outset she placed the school upon a high plane, claiming for it a genuine educational status, requiring definite and appropriate educational methods, and assumed the title, not only of Superintendent of Nurses, but of Principal of the Training School. The usual course of training at that period was one year followed by a second year of experience in private families. The training might be said to be compulsory, while instruction was frequently elective, dependent upon the student's desire, or the exigencies of the hospital.

Miss Hampton extended the course of instruction throughout the second year; she amplified it, systematized and graded it. She introduced new subjects, such for instance as instruction in dietetics and invalid cookery; she secured opportunities for practical training not offered then in The Johns Hopkins Hospital. Training, for example, in the care of infants was gained at the Mt. Wilson Sanitarium. Attendance at lectures was required; careful note-taking with systematic examinations and tests was instituted. The custom everywhere prevalent then of sending students out into private families during their second year was rejected utterly. The equally prevalent custom of placing students in charge of important wards and other departments was similarly disposed of, and carefully selected graduate nurses were placed at the head of each department.

In doing all this Miss Hampton had not only her own creative energy and ideals to carry her on; she had also the active and sympathetic support of the entire administration. Francis King, then president of the board of trustees, was her warm friend and adviser; and his daughter, Elizabeth King Ellicott, whom we sadly miss here to-day, took up his interest where he laid it down, and was one of the staunchest friends the training school ever had. Dr. Gilman, president of the university, and guardian of the hospital in its infancy, was unfailing in kindly interest and sagacious advice; while no one believed more sincerely in the mission of the training school than Dr. Hurd, the superintendent of the hospital, and no one was more ready to forward its educational work. The cooperation of the medical staff was generous. The members of that first little group of students, of whom the speaker was one, like to remember that their introduction to the mysteries of the human body came through Dr. Councilman; that theories of infection and immunity were presented by Dr. Welch and later by Dr. Flexner, with a simplicity and clarity that reached even their "terminal facilities"; that certain aspects of medical diseases were made known to them by Dr. Osler, coupled perhaps with sundry exhortations of a strictly personal nature. Some of them still treasure their note-books; all of them treasure these memories.

There was one other in these early days, a woman of rare character and qualities, who as assistant and teacher filled a large place in the school for several years. Independent, fearless, loyal, Lavinia Dock exercised unconsciously an influence which was both strong and enduring, and few con-

nected with that early life had more to do in the last analysis with shaping ideals and giving direction to future activities than this beloved teacher. A student and a thinker with a mind of a peculiarly fresh and original cast, with ideas clear-cut and logical and considerably in advance of the time, there were few of the problems of the training school or hospital, or of the professional life of nurses, to which she could not give illuminating thought. She had an extraordinary way of driving directly to the heart of a matter, pulling out the essential facts in the situation, and showing us the right way to think about them and to deal with them. Her sense of justice was keen, but her sympathies were well-nigh boundless. It has been her chosen task to write of the lives and deeds of nurses in many fields, and she has written the history of this training school with such characteristic self-effacement that no trace of her own years of rare work with us can be discovered. It is important that her share in the upbuilding of our school should be well understood.

Under Miss Hampton's able and fearless directions, and with the assistance and cooperation of those who have been mentioned and others, conditions were built up which made the school a center of interest. It soon took a commanding position among the schools of this country, and its influence extended widely into other countries. It was looked to for all that was best in training-school work, for liberal and progressive ideas, and for informed and correct methods.

The school did much to break down the "splendid isolation," that heritage of cloistered and military ideals, which had hitherto been built up about hospital training schools. It created conspicuous traditions of hospitality, and marked courtesy was shown to all visitors from other schools. Every opportunity was granted them for a study of methods worked out here which might be helpful elsewhere. Every effort was made to establish cordial relationships and to sweep away a narrow and exclusive attitude in training-school administration. The heads of this school constantly studied progress made in other training schools, and in other branches of education.

After five years of extraordinary activity, during which the school was brought forward steadily in every aspect of its work, large ideals of nursing had been established and a fine spirit of fellowship had grown up in the school and in the *alumnæ*, the woman who had so nobly planned and achieved gave up her work and was succeeded by a graduate of the school, who had been her assistant. The broad lines on which the school should develop had been outlined during those years; possible developments had been foreshadowed. The tasks, therefore, which confronted her successor were principally those of continuing at its high level an administration of conspicuous efficiency, of maintaining standards of work already high, and of carrying forward loyally oft-discussed advances with which she was already in the heartiest accord.

Miss Hampton had planned the extension of the course from two years to three, the reduction of the hospital day from nine hours to eight, the abolition of a regular money allowance to students, which was customary in all schools, and the application of the sum so released to furthering the educational

work of the school. These measures, radical in their nature, were all shortly carried into effect with great resultant benefit to both school and hospital. The obvious advantage of having a body of students for three years in training was quickly recognized by hospitals throughout the country, and the majority of them hastened to lengthen the training period, often, to our regret, without regard to other conditions which should accompany, and would justify such a change. The introduction of the eight-hour day has proceeded much more circumspectly.

A few years later another step forward was taken in the establishment of what is called a Preparatory Course of Instruction, in which prescribed elementary scientific and technical teaching is required before the student may be admitted to the hospital ward. The idea, which had its origin in England, but was very slightly developed there, was here carefully worked out, placed on a dignified and substantial basis, and has been accepted as a considerable advance in educational methods. It has been widely introduced into training schools, but has hardly as yet anywhere reached its possible development.

Among other important advances which this school has made, was the establishment of scholarships, and it was, I believe, the first training school to recognize the value of such stimulus to effort. We welcome almost annually among the students in our college of Columbia University a Johns Hopkins nurse, who, as the holder of one of these scholarships, is enabled to secure a year of college work. The example of this school has done a good deal to awaken similar interest in other schools.

Again, the school took up new ground when, in 1900, it decided to require tuition fees from students for a part of the first year's instruction, thus establishing the principle that instruction in training schools should be paid for by students precisely as it is in other schools. The idea has made some headway, and eventually, probably, such measures will be carried further, as one of the important ways through which necessary improvements in training-school work may be brought about.

Advancing further along the same line, the school began to pay for instruction and to place some of the various subjects in the hands of carefully selected and salaried lecturers and teachers. Only those who have carried on a school where every course of lectures was somebody's kindly voluntary contribution, and nobody's regular stipulated task, can realize what this particular reform means. The custom of paying proper fees or salaries to lecturers and teachers has now been adopted in a good many leading training schools and is growing steadily.

To the literature of nursing, the staff and graduates of the school have made notable contributions. The *Principles and Practice of Nursing*, published by Isabel Hampton in 1893, was the most comprehensive text-book on that subject which had so far appeared. The *Handbook of Invalid Cooking*, by Mary Boland, was the first substantial work on that subject. The *History of Nursing*, while published later under joint authorship, was very largely the work of one, Miss Dock, who had also some years before contributed the first *Materia Medica for Nurses*. A handbook on Visiting Nursing in the United

States, by Yssabella Waters, was the first attempt to classify and arrange for reference material on this subject.

Within the twenty-five years of its life there have been but three changes in the administration of the school, which has felt itself fortunate that in each instance the choice of a superintendent has been from its own graduates. "Rank Chauvinism," Dr. Osler would probably say, were he here; but he would, it is hoped, concede that its usual dire consequences had somehow as yet been averted. For the usefulness of the school has grown steadily; it is vigorous and flourishing; it holds a position of unquestioned importance in the nursing world; it is still looked to, not only for standards of work, but for light and leading on the many problems, old and new, of training-school work and administration, of hospital and community relationships, with which nursing anywhere at present is beset. The moral influence alone which it is able to throw into the scale where important issues are being weighed is a power so great that it carries with it a peculiar responsibility. Neither this school nor other schools can afford to have it diminish. It has been, for instance, of decisive value to be able to point to the attitude of The Johns Hopkins School on the question of hours of duty in places where the struggle for an eight-hour system was going on.

The work of the school has increased greatly both in volume and in difficulty, as large new hospital departments have been added, but this must be somewhat offset by the enormous advantage it is to the school to be able finally to offer to its students training in the Children's Hospital and in the Psychiatric Clinic, and eventually perhaps in the Social Service Department. There is now, I understand, no branch of modern nursing in which the school is not prepared to give admirable instruction and training, and recently it has taken the wise step of opening up opportunities in its important new departments for post-graduate training. The little group of seventeen students of twenty-five years ago has grown into a student body of about two hundred. (In view of the excellence of the opportunities here offered, the speaker wishes it numbered four hundred.) There were then seven members of the administrative staff; there are now about fifty.

The school has graduated between six and seven hundred students now widely scattered through this and other countries. Looking at the general high character of this body of women, recognizing the sound quality of their professional work, and knowing well the rare and valuable services in special fields rendered by many of them, one becomes impressed with the way in which the school has served the purpose for which it was founded. Visions of some of these women and of the work they have done and are doing arise. One thinks of Miss Noyes and the stupendous burden which she carries as the head of one of the greatest of municipal training schools, historic Bellevue in New York, which gave us our Isabel Hampton; of the twenty years and over of devoted and valuable service which Georgia Nevins has rendered in the upbuilding of the Garfield Hospital, Washington; of Ada Carr and Mary Lent and of the work in the poorer districts of Baltimore which they have built up, of the honorable place which that work holds in the opinion of

the public, and of the affection in which they personally are held; of Carolyn van Blarcom and her excellent contribution to work in the prevention of blindness. Her recently published study of Midwifery is accepted as a valuable addition to the literature of that subject. And in other countries one sees Grace Baxter, at her solitary post in the old hospital in Naples, holding up, against the traditions of centuries, modern standards and ideals in nursing; while in the Far East Etha Klosz is editing the Nurses' Journal of India, inspired by love of her work, to add thus to the cares of her household and her small family. Many other names come to mind of those who have done equally noteworthy work. The list is long and time is fleeting; but this may with some confidence be said, that they are usually swift to acknowledge their indebtedness to this school and hospital for almost all that they have been able to accomplish. In hospitals, in training schools and in various forms of public-health work about one hundred of our graduates now appear to be occupied. A study of this group shows them in the main to be a body of able, high-minded and progressive women, a genuine asset to any community in which they may be placed. Through these workers the influence of the school is extending widely in many directions. Roughly speaking, about 25 per cent of our graduates have married and thus doubled their influence wherever they may be. They are among our most public-spirited and devoted members. The influence, in fact, of the school in this direction would be looked upon as unusually excellent and far-reaching, though candor might compel the admission that it has been unconsciously exercised.

While a large proportion of graduates, about 35 per cent apparently, are engaged in private nursing, it seems evident that the number so occupied is diminishing. It was calculated that at least 75 per cent of all nurses graduated twenty-five years ago, entered upon such private work. The growing tendency on the part of all classes to go to hospitals in illness seems to be carrying the private nurse out of homes and into a special form of institutional work. There is clearly a change taking place here that is worthy of attention from training-school authorities. The changing status of the nurse in private work, and the tendencies which are bringing her in as a worker under municipal or state control, give a different cast to her activities and provide an entirely new outlook for her which will probably eventually have a considerable bearing on methods of education and training. The idea, for instance, of a corps of nurses in the public schools was undreamed of when this system of training was established. Yet they are now found by hundreds in schools, city and rural, throughout the country, and are in places being pressed into the teaching force, as instructors in elementary personal and practical hygiene.

The Alumnae Association, of which a very large proportion of the 660 graduates are members in good standing, was formed very early in the history of the school. It has been of inestimable value in binding the graduates together in good fellowship, and for united effort in maintaining good professional ideals. It has established a club, and a successful registry, has

built up funds for the protection of its members, and has been a generous contributor to various outside educational philanthropies. It has recently given about \$2000 to the Isabel Hampton Robb Educational Fund, which provides scholarships for the higher education of nurses. It has for years published a magazine of an excellent type.

Measured by its immediate contemporary usefulness, the training school is one of the most important institutions which this city holds. In your greatest hospital it binds closely together all the departments in an ordered life and carries forward, day and night, work of paramount importance to human welfare, to medical teaching and to scientific advance. In the greatest crises of life, both in this hospital and in your homes, the school plays through its graduates an increasingly beneficent part. Measured by its wider usefulness, the school may be truthfully said to have exercised an influence upon the education and training of nurses in this country, which has been remarkably wholesome, helpful and stimulating. It has constantly striven to hold up ideals of professional life and work, and to dignify its status.

As one who has known the school from three standpoints, first as a student, then as an officer of the school and hospital, and finally as its head for many years, I feel that one less intimately connected with its history might give a clearer picture of its growth and influence, and I am conscious that my most serviceable opinions have come as the result of seven years of anxious and affectionate interest, as a kind of bystander. In looking backward upon the splendid quarter of a century of work accomplished, of difficulties met and conquered, of continuous and inspiring progress, my affection and admiration for the school are renewed and strengthened, and I see her now bending her energies to the solution of new problems and building as nobly in the future as she built in the past. Some of the largest and most fundamental problems in nursing are as yet untouched. Take one of them: there is not one single endowed training school in the whole wide world. All training schools are self-supporting institutions, and most of them are ample contributors to hospital support. This should not be. A sounder economic basis eventually all schools must have. Every training school should have its own appropriation, prepare its own budget, and be accorded an established and dignified economic position. The principal of any training school should know, just as the head of any college department knows, how much money is to be at her disposal during the year, and it should be sufficient for the educational work she is held responsible for doing. The hospital should not be constantly under the painful necessity of weighing every request from the training school against obviously needed things, improvements or appliances which are the very life of the hospital. Could the twenty-fifth anniversary of The Johns Hopkins Hospital Training School be more appropriately or more justly celebrated than by beginning to provide her with a suitable endowment? For whatever direction the future of nursing may take, nothing appears to be more certain than that it will increase in opportunities for public service of a varied, unusual and important nature, and that the education and training of

nurses for such service cannot remain cast in an unchanging mold. Nor can it change greatly until we abandon the gospel of utility, and establish a new one, the gospel of freedom. The necessity of endowments for training schools was eloquently urged by Dr. Hurd a few years ago. How fitting it would be to have this school lead the way in this essential advance. Our large and important body of alumnae could render no higher tribute to their school than to help it to serve better the profession we all so love and cherish.

Dr. W. H. Welch, Baxley Professor of Pathology, The Johns Hopkins University, and pathologist to the Hospital, spoke in part as follows:

ADDRESS OF DR. WELCH.

I wish to express my great regret, and I know it is a source of deep regret to all, that Dr. Osler is not here, because in consequence of his absence I occupy what would have been his position. I received only this morning a message from Dr. Osler (he will never be quite Sir William to us here in Baltimore) conveying a greeting:

Greeting to all old friends and pupils.
Am with you in spirit.

OSLER.

I wish to express in behalf of all my colleagues the exceeding joy we have in the return of so many members of the staff of the Hospital and of the graduates of our School. Our dearest possession is the work of these men, and the most significant characteristics of this celebration is their return on this occasion.

Much that I might desire to say has already been touched upon. I will add a few words as to what went before the opening of the Hospital and the situation which existed at that time. We had first of all a generous endowment, which enabled the Hospital and School to do a work only possible thereby. In the letter of Johns Hopkins to his trustees, we also had that most memorable sentence already quoted:

You will bear in mind in all your work in relation to the Hospital that it is my desire and purpose that this institution shall be a part of the medical school of that university for which I have amply provided in my will.

That is the key note, and it remains the key note in all that has been done in the Hospital and the Medical School, and I think we may fairly claim that the wishes of Johns Hopkins in this regard have been fulfilled by his trustees and by those working in the Hospital and the School. When one stops to consider that these words were penned by a layman in the year 1873 when medical education was at a fearfully low state in this country, and how even today they would be remarkable, it is well for us to pause to pay tribute to the extraordinarily enlightened sentiments of this beneficent donor.

Throughout the construction of the Hospital, the conception of Johns Hopkins that it should be a part of the future medical school, was never lost sight of, and all honor to that great man, Dr. Billings, who advised the trustees so intelligently in all of these matters. Most significant for the future

of the University and Medical School was this association with the Hospital.

The University, through President Gilman, had already done a work for higher education which constituted the foundation and ideal of the future Hospital and Medical School. President Gilman was singularly interested in medicine. In planning the work and character of the University, he constantly had in mind the needs of the future Medical School. The principal address at the opening of the University was by Huxley, and no small part of it related to the problems of medical education. The sciences fundamental to the study of medicine—physics, chemistry and especially biology—were provided for amply and most fortunately by President Gilman by the choice of Rowland, Remsen and Newell Martin. I must pay tribute to the work of Newell Martin who did so large a service to the development of biological science in this country. He created an atmosphere here which has continued to this day to pervade our thoughts and spirits. We owe to him a debt of gratitude hardly to be expressed.

Through the work of President Gilman, a good deal of cumulative knowledge and literature had been obtained as to the plan of the Medical School. One of the first things I was asked to do when I came in 1884, was to outline what I conceived to be the best organization of the Medical School. The work of the pathological laboratory began in 1885. It was opened first in the biological laboratory and later in 1886 in one of the Hospital buildings which had been completed for the purpose. This was occupied by myself and my associate, Dr. Councilman, who was already here when I came and proved a great inspiration and stimulus to all.

I must pause to consider those first years of work in the pathological laboratory, before there was a hospital. The first Fellow in Pathology was Dr. F. P. Mall. At the same time Dr. W. S. Halsted was engaged in experimental work. Dr. Christian A. Herter was also a research worker. I would further call to mind that before the Medical School was started, there were in the laboratory, Flexner, Abbott, Blumer, Walter Reed and others. The list is too long to be given here.

The state of medical education when the Johns Hopkins School was started was most favorable for the development of such a school as we had in mind. As early as 1880 there had been efforts to improve the character of the medical schools of this country. We cannot look back except with sorrow, at the state of medical education during the early part of the nineteenth century. By 1880, Harvard Medical School, the school at Ann Arbor and a few other medical schools had already taken steps to improve the standard. There was consequently an eagerness on the part of the medical profession to see the establishment of a school of a higher order than any which existed at that time. We felt that to add one more similar medical school to the list of those already existing would be of little service to the community or to the country, or to the cause of medicine.

At the end of that wonderful decade, 1880-1890, perhaps the most wonderful decade in the history of medicine, there

had been a revolution in medical thought through the discovery of the agents causing infectious diseases,—such discoveries as the bacillus of tuberculosis, of Asiatic cholera, of diphtheria, of typhoid fever and other infectious diseases. Those living today can hardly realize the enthusiasm and youthful spirit which was stirred not only among medical men, but in the general public by these discoveries.

It has already been stated that the Hospital was opened in 1889, four years before the Medical School. Dr. Osler was called in 1888, and Dr. Halsted was already here. Dr. Kelly came soon afterwards. However, there had been the nucleus of a medical faculty from the early years and meetings of the medical faculty in fact were really held before the opening of the Hospital. We were disappointed that the Hospital should open before the Medical School had started, but as I look back, I agree with Dr. Hurd that this was doubtless a distinct advantage. I cannot attempt to elaborate the points suggested, and will only call your attention to the fact that the character of the organization of the staff of the Hospital was probably determined by the fact that there was no medical school. That organization remains today one of the most distinctive features of the Hospital. You recall that we speak of the resident house staff frequently as our upper staff. It consisted of men selected by scrutinizing the available candidates, wherever found, and appointing them for indefinite periods, many in fact remaining for several years. Dr. Thayer came in 1890, and succeeding in 1891 the first resident physician, Dr. Lafleur, remained on the Hospital staff in the same capacity for eight years. The significance of this fact is that we thus afforded opportunities for training in the higher departments of medical work, similar to those afforded in laboratories for training in the sciences. It differs from the system of rotation in vogue elsewhere, and has been one of the great sources of service to the Hospital, in that young men of great promise have been attracted here by these unusual opportunities. The list of those who have been resident physicians, surgeons, gynecologists and obstetricians will help you to realize that this has been one of the distinctive features of our organization. Such provision for the higher grades was in large measure due to the fact that the Hospital was started before the Medical School opened. The Hospital was therefore an educational institution.

Dr. Osler has pictured the spirit of those early days, so I shall not attempt to add anything to what he has said. All who are here today from those early years feel that there was an environment, an atmosphere and ideals which will always be cherished and will continue to be an abiding influence.

As I have said, it was a disappointment that we could not start the Medical School at the time the Hospital was opened, because the trustees felt that the endowment of the University could not assume the additional expense, and that an additional endowment of \$500,000 was required for the purpose. This endowment was raised, largely through the efforts of Miss Mary Garrett. We owe a great deal to Miss Garrett and to the women of the country who contributed to this fund.

In Miss Garrett's letter to the trustees there were two conditions; one as to standards of admission and the other as to co-education. As regards the standards of admission Dr. Osler expressed the situation when he said to me: "Well, we are lucky to get in as professors, for I am sure that neither you nor I could ever get in as students."

We had no formal opening of the School. We feared to call attention to our institution lest we might have no applicants for admission. However, we opened the School with seventeen students and graduated fifteen of them, most of whom I see here today.

We were somewhat disturbed by Miss Garrett's condition relating to the admission of women. It was a more startling proposition at that time than it would seem today. However, I regard it as a distinct advantage to the Medical School that we have women students here, and if we were not bound by the terms of Miss Garrett's gift, we should make no change in that regard.

Let me mention what I consider to be some of the more distinctive features of our Hospital and School, some of which I think can be considered as real contributions to hospital organization and medical education. I should place among the first our demonstration of the value of a teaching hospital in association with a university. Patients get far better care in such a hospital. The presence of students in the wards of a hospital is seen to be an advantage in studying disease, in accuracy of diagnosis and in better and more successful treatment of disease. There can be no question that a hospital available to students is the best kind of hospital, from whatever point of view you look at it—whether from the welfare of patients, the advancement of medical knowledge, or contributions to science. One of the most serious problems today in this country is the establishment of such relations as exist here, between hospitals and medical schools which have developed independently of each other. This was never a problem to us.

As Judge Harlan has stated, we have no regulations as to these relations. When inquiries come as to our own regulations and rules in order to fix similar relations between other medical schools and other hospitals, we are somewhat embarrassed. The relations of the trustees of the Hospital to the staff and to the faculty are almost ideal. The trustees are ready and eager to listen, and if in their power, to accede to the requests of the Medical Board.

The fact that the Medical School has been an integral part of the University is also important. Here a member of one faculty is on the same footing as a member of the other. The fundamental medical sciences are on a true university basis. The wisdom of that was first demonstrated at Harvard, in the establishment of the department of physiology—a most notable contribution. Here all the important fundamental subjects—anatomy, pharmacology, physiology and chemistry—are in charge of full time men, and have freedom to develop.

The organization of clinical teaching, we owe to a large extent to Dr. Osler. Its most distinctive and useful feature is the admission of students to the dispensary and to the

wards of the hospital. Patients are assigned to students, who are thus given opportunities to study disease which previously existed solely for internes. Our whole method of teaching was to a large extent a reaction, which may have seemed almost too sweeping against methods previously existing. In a way it has done away with didactic teaching. At any rate, the whole atmosphere of the place has been that of practical teaching, both in the laboratories and in the wards.

All of this, however, relates merely to organization and to providing opportunities for study. The real results are not there. They are to be sought in the life of the institution, in the men connected with it and those who have gone out of it. It is seen also in the spirit of love and harmony which prevails, in the concession of the right to each individual to develop, and in the spirit of research. We are here, as one has expressed it, like a family.

I must pause to mention briefly one of the results of the work in medical education, organization and research. If we had not followed such paths, I question if an institution like the Rockefeller Institute for Medical Research could have been founded. If I were to speak of the work of those who have been connected with the Hospital, many names would suggest themselves, but they are familiar to you all. It is really the work of our graduates which constitutes our most enduring monument. Up to this time, one hundred and thirteen graduates of the medical school bear the title of professor and many more are engaged in teaching.

It would be interesting to say something about the growth of the Hospital since its foundation, of the new departments due to the generosity of various benefactors,—the pediatric clinics, the Phipps clinics, the urological institute. I had also intended to touch upon some interesting features of our recent development, namely the limitation of the size of the classes in the Medical School, and especially upon the plans for placing certain departments of the Hospital upon the university, or so-called full-time basis. I will simply say that the latter came about through an application made to the General Education Board on behalf of the School by the trustees of the University and the Hospital, and that we heartily believe that we have a splendid opportunity to demonstrate the value of what we conceive to be a great reformation. There is to be provided a staff of professors with assistants in the departments of medicine, surgery and pediatrics to give their entire time to the work of the Hospital and the School, not cut off from private practice, but relieved of the difficulties arising from it. Neither Dr. Barker nor Dr. Thayer felt they could accept the position under the new terms, but we rejoice that they remain with us, co-operating in this scheme, and continuing their services to the School and Hospital. We consider ourselves fortunate that we have been able to secure Dr. Janeway as the head of the department of medicine, under this new arrangement. He is enthusiastic and sympathetic, and we are looking forward to the larger opportunity which has been placed in our hands by the liberal-ity of the General Education Board.

I had intended to say a few words about our needs, for

we have serious needs, but the hour forbids. This afternoon we have looked back on what we have accomplished. It should turn our minds to the future. In the past we found much to inspire us; we look confidently to continued growth, to the preservation of ideals already established, to the future development of the Hospital and Medical School and to the training of young men and women for careers of usefulness in the relief of human suffering and in the promotion of general welfare.

Dr. Winford Smith, Superintendent of The Johns Hopkins Hospital, spoke as follows:

ADDRESS OF DR. WINFORD SMITH.

The purpose of these remarks is to convey to you some idea of the hospital as it is at present and the possibilities of the future.

The Johns Hopkins Hospital, when opened twenty-five years ago, provided accommodations for some 250 patients. The bed capacity was soon increased to 362 by the addition of the colored wards, the utilization of a part of the isolation ward for a lying-in ward, and the ground floor of this unit for similar purposes, and an addition to the gynecological ward. For many years, in fact until two years ago, the capacity remained at 362.

Although this would not seem to indicate a very rapid growth, nevertheless there has been a continuous, steady growth in activities—a constant broadening of the field of work. The machinery for caring for even 362 patients is much more complex, the methods infinitely more skilful, more time-consuming and more costly than was the case twenty-five, or even ten years ago.

Public sentiment regarding hospitals has undergone great changes. The hospital is no longer considered the place of last resort, but the place of first resort in time of serious illness. In consequence, the demand for hospital accommodation has constantly increased, both for admission to the wards and for treatment in the out-patient department or dispensary. This has made it necessary to select patients with greater care each succeeding year, in order that the hospital, since it could not serve all, should at least serve those whose need was most urgent and who were most worthy.

During the past two years, both the scope of the work and the size of the plant have been markedly increased. The Harriet Lane Home for Invalid Children, while at present operating to only one-third of its capacity because of insufficient funds, provides accommodation for 100 children needing medical treatment. The Henry Phipps Psychiatric Clinic, complete in every detail, with its wards, laboratories, class rooms, gymnasium and recreation rooms, added 88 beds. The Charles L. Marburg Memorial Building, containing 56 private rooms and a large and beautiful dining hall for the hospital staff, while increasing the capacity only 15, did more by furnishing infinitely better accommodations and by releasing former Ward B to be used as an annex to the Nurses' Home for the accommodation of 75 nurses. The James Buchanan

Brady Urological Institute, soon to be occupied, adds 60 beds and provides research laboratories and examination rooms, and extends the facilities of the dispensary. Furthermore, it is the first clinic of its kind in America.

Many other changes have taken place, without which this great increase in activities would not have been possible. For example, a new and larger laundry, the remodeling and re-equipment of the kitchen, a new heating plant, a domestic building for women employes, a fifth floor to the pathological building, and others of lesser importance.

We find then, at the end of twenty-five years, a hospital of 625 beds as compared with 250 at the beginning. Johns Hopkins, in his letter of instructions to the board of trustees, dated in May, 1873, wrote the following:

It is my wish that the plan thus chosen shall be one which will permit of symmetrical additions to the buildings which will first be constructed, in order that you may ultimately be able to receive 400 patients, and that it shall provide for a hospital which in construction and arrangement shall compare favorably with any other institution of like character in this country or in Europe.

The plant which originally represented an investment of \$2,068,351.05, now represents \$4,390,218.46. You can form no adequate conception of the growth from a consideration of these figures alone. You must understand and appreciate the growth in every direction, the broadening of the scope, as well as the increase in the amount of work, the improvements in methods, the contributions to knowledge by members of the staff, and the increase in the number of doctors, nurses and employes.

It may be of interest to note that the hospital family of doctors, nurses and employes and patients numbers some 1100, not including the 300 patients treated daily in the dispensary. There are now 227 nurses in the training school, 60 physicians and surgeons living in the hospital, and 125 more working in the hospital, but living outside. During the twenty-five years, 96,000 patients, requiring 2,000,000 days of treatment, have been received in its wards, and 1,600,000 visits have been made by patients to the dispensary. The cost of operation has been \$6,267,330.57, and of this sum \$3,334,660.70 represents the amount spent on free treatment. This year 6000 patients will have been received in the wards and 25,000 in the dispensary, all at a cost of about \$500,000. Sixty per cent of all patients admitted are treated absolutely free of charge.

In gauging the real growth and real worth of the hospital you must consider not only its size and the number of patients it serves, but also its influence on the community, the value of its teachings, the men whom it has sent forth to do important work elsewhere, the value of its training to the 90 young men and women who go out each year to practice their profession, the value of the 15 or 20 trained physicians and surgeons and the 40 or 50 nurses whom it sends forth annually. That more than one thousand young men and women graduating from the medical school have received their practical training in this hospital, that 350 physicians and surgeons have served on the staff in acquiring additional skill, that its training school has

trained more than 600 nurses, stands as a great service to suffering humanity.

Dr. Billings, in his address at the opening of the hospital, said: "Hospitals are in some sort the measure of the civilization of a people, but a hospital of this kind should be more than an index. It should be an active force in the community in which it has been placed." Has the hospital measured up to this?

A Baltimore daily paper answered this question three years ago in referring to the hospital editorially as follows:

One cannot express the good such an institution as The Johns Hopkins Hospital does, in cold figures or terms of dollars and cents. The hospital is one of the glories of Baltimore. Its growth is the result of a noble devotion of the men (of its staff) to the cause of humanity; its reputation lies not in the number of its patients and its size, but in the observance of the highest standards of medicine in the treatment of rich and poor alike. The 80,000 patients who have found needed relief in its beds, the million and a half who have been given aid in its dispensary, and the fathers, the mothers and the children of all these, constitute a tremendous army of witnesses to the value of that charity.

In speaking of the future we can only draw a picture which will represent the hospital enlarged sufficiently to meet the demands upon it, a picture which will portray the possible fulfillment of our hopes, born of our present needs.

The needs are urgent in many directions. Two more public wards of 30 beds for the treatment of white women in the departments of medicine and surgery are urgently needed. Two wards, each containing 30 beds, are required for the reception of both white and colored children requiring surgical aid. The Harriet Lane Home will take care of those needing medical treatment, but the facilities for surgery are almost entirely lacking. Another ward for white men needing medical treatment could be filled at once.

The lying-in ward is not only overcrowded and inadequate, but some of the space used was never intended for patients. The old wards should be completely remodeled and sufficient space added to bring the capacity up to 50. Whether this should be continued as a separate unit, or united with gynecology to form a *Frauenklinik*, is a question which the future will decide. A ward or wards for the specialties, for the treatment of diseases of the eye, ear, nose and throat and skin, has always been needed but never supplied. That at least 60 beds are required for this, is each year more apparent.

The importance of the out-patient department, or dispensary, is too often overlooked. The Johns Hopkins Hospital Dispensary serves daily some 300 patients in accommodations long since outgrown, even though it is open all day. A new building for this purpose, large enough to permit all departments to be open at the same time, would harmonize the work, make it possible to serve more patients and prevent the great loss of time to both physicians and patients which now occurs.

The hospital library has been inadequate for years. The shelves are full and the cellar too. A new building large enough to accommodate both the hospital and medical school libraries is something which we trust the future will provide.

Then there is needed a convalescent branch, which is of

prime importance, and which I have left until the last that its need might be more apparent; but in the construction of additions, it should come first. Johns Hopkins foresaw this as long ago as 1873 and referred to it in his letter to the trustees.

A convalescent branch of 100 beds, suitably located to furnish country air and scenery and easily accessible, would relieve for some time the congestion in the main hospital, and at the same time extend the work with greatest benefit to the patients and at the lowest cost. A beginning has already been made in this direction. The Johns Hopkins Colored Orphan Asylum, until recently operated as an orphanage entirely, will in the future be utilized not only to benefit the colored orphans, but will provide 40 beds for convalescent crippled colored children, who will first be given surgical aid in the hospital, and subsequently be transferred to the convalescent wards at the orphanage. It is an important step and will undoubtedly render a much greater service to the colored race. By early correctional treatment, and by school training during long convalescence, many who would otherwise grow up helpless or seriously handicapped, will thus be made capable of self-support.

To accomplish even a part of all this means another addition to the nurses' home, which is now full, even with former Ward B as an annex. The nursing staff is the backbone of the hospital and must be properly provided for.

When these additions shall all have been made, The Johns Hopkins Hospital will accommodate 900 patients instead of 625 as at present, and its total population will approximate 2000. This should be the maximum, for beyond this the institution would be unmanageable and uneconomical in administration.

You may wonder where it will be possible to place these additions. No more ground is needed. The foundations of the present ward buildings will carry two more stories. The needs outlined above represent nine more public wards, and they can easily be added to the present ward buildings, thus converting the present single-ward pavilions into pavilions of three wards each. This arrangement would permit of a concentration of the several services, which would much facilitate the work and increase the efficiency of the plant.

The new library building should be located on the Wolfe Street side; and the new building for the dispensary, four or five stories in height, should extend from the present surgical building to Wolfe Street, and should provide sufficient space, properly arranged, to permit the operation of all departments at the same time, laboratories for routine work and for teaching, and an admission ward for the reception of patients at night, in order that the disturbance of the hospital wards which now results might be avoided. This building should also provide what has long been needed—a section containing ample space and modern equipment for the department of pathology. Such a building, it is obvious, would provide for the proper co-relation between the different laboratories and between the wards and laboratories.

Does this seem too visionary?—to be asking too much? It might well seem so. Yet I have only sketched for you the physical additions to the plant which we know to be demanded

even now. A hospital must grow to meet the demands of the community if it is to attain to its greatest usefulness. Of the changes in organization, in character of service, in scope of work, which will undoubtedly occur, I need say little. That the same high standards will be maintained, that the same enthusiasm, the same harmonious atmosphere will prevail, that continuous improvement in methods and technique will continue as in the past, may be taken for granted. Indeed, with the new system of full-time service in operation, conditions should be even more favorable; otherwise the changes will not have been justified.

In closing may I remind you of one thing? Great was the generosity of Johns Hopkins, when he conceived and provided for the institution which bears his name; wisely did he select his trustees, who with remarkable foresight and breadth of vision have executed his trust from the first board down to the present. But if, through the years, The Johns Hopkins Hospital has enjoyed an enviable reputation, if its success has been above the ordinary, if it has stood out prominently as an example of excellence—this has been due not alone to the wisdom and generosity of its founder and other benefactors, or to the successive boards of trustees, or to the millions invested in the plant, but to the men and women who were selected to inaugurate and carry on the great work—Doctors Welch, Osler, Halsted, Kelly, Hurd, Miss Hampton, Miss Bonner and Miss Nutting. To these few who organized the work, created standards and ideals, and to those others, their associates and assistants, who were trained by them and who have continued their work here, or have carried those ideals elsewhere—to these in no small measure belongs the credit of whatsoever of unusual merit has been the product of the past twenty-five years.

For the future, we still have Doctors Welch, Halsted, Hurd and Kelly; and as to the others, if enthusiasm, a strong faith and devoted service are to count, then the future is safe!

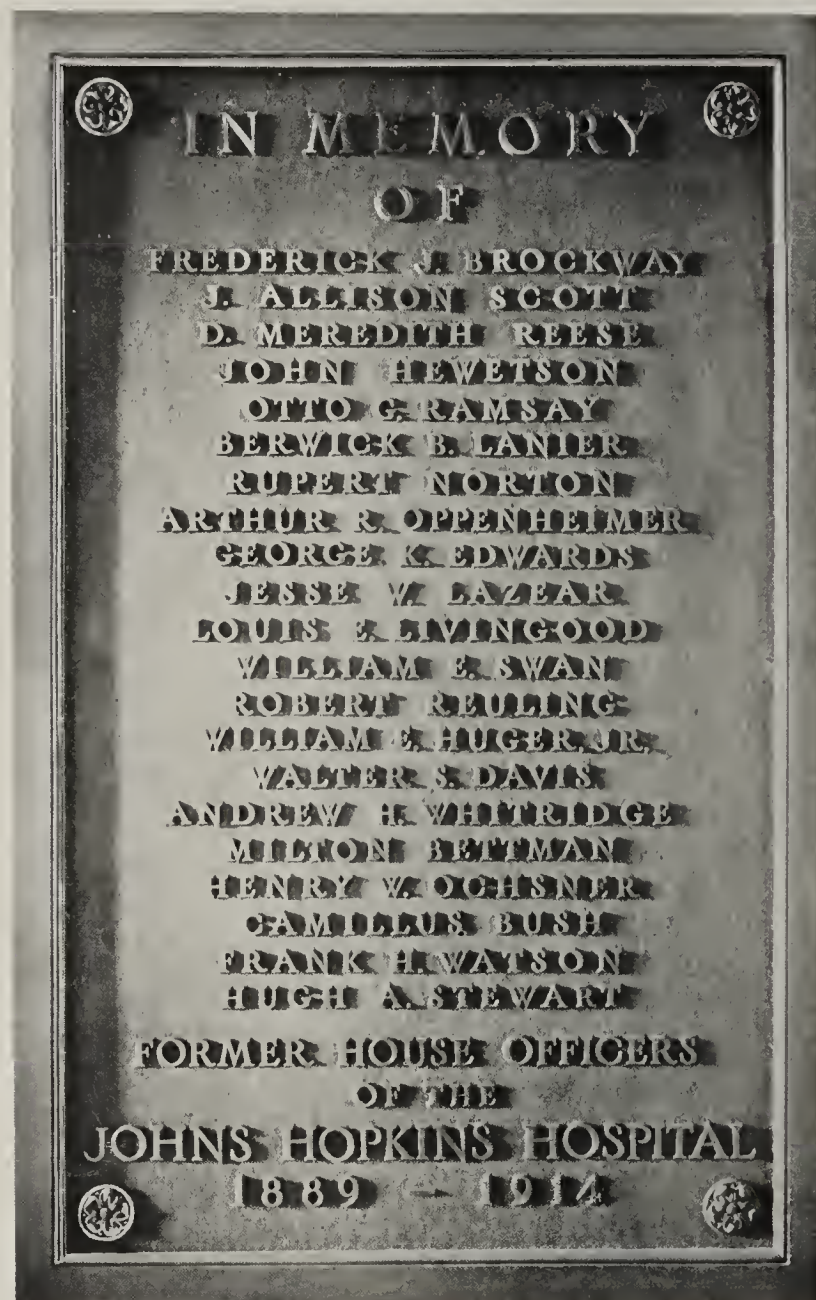
PRESENTATION OF TABLETS, PORTRAIT AND
MEDALLION AT THE HOSPITAL
OCTOBER 1.

Dr. Hurd first presented a tablet which had been placed in the rotunda in memory of deceased resident and assistant resident officials of the hospital, with the following words:

REMARKS OF DR. HURD.

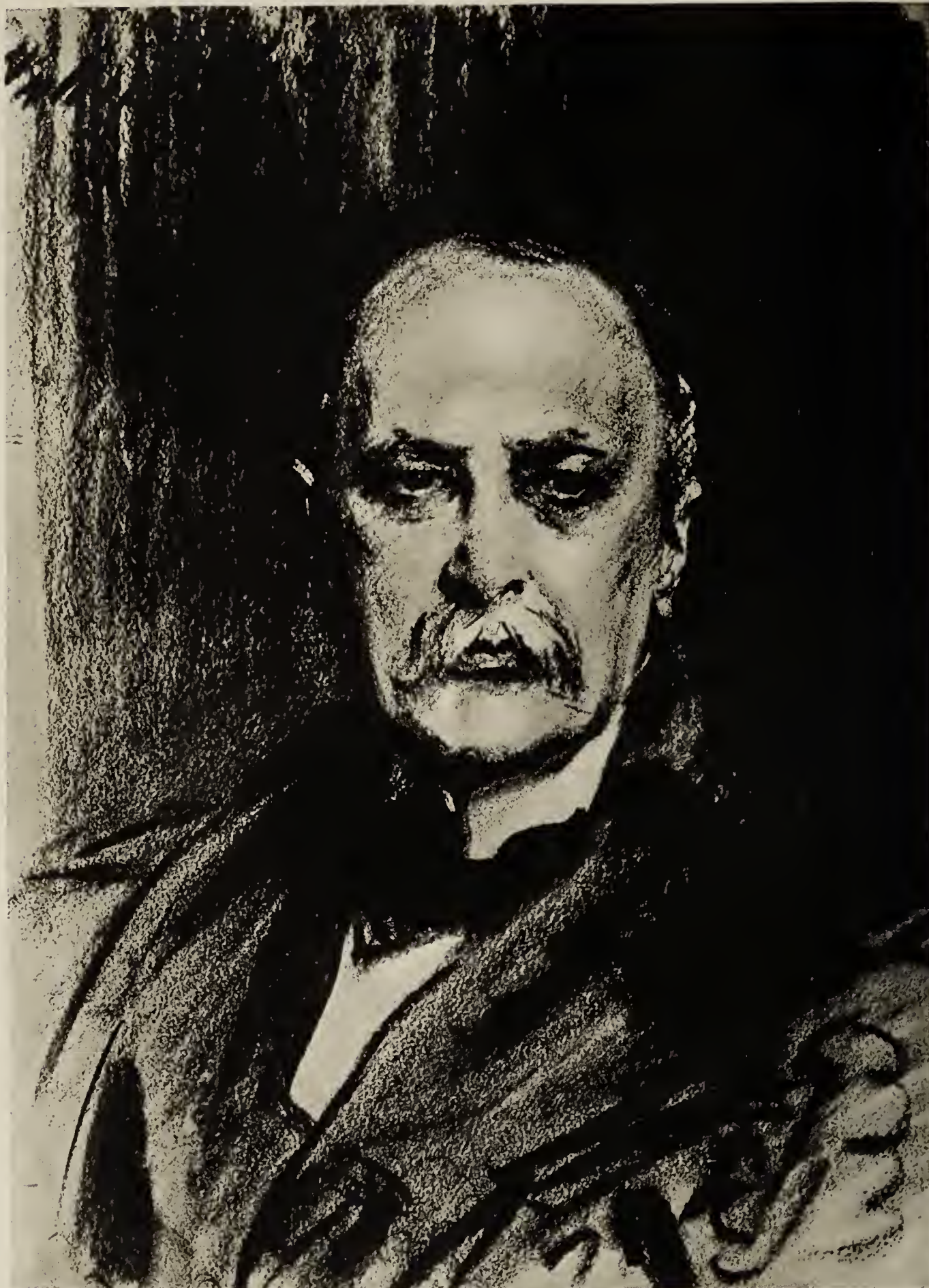
The problems of life and death are ever present with physicians. All human beings come into this world without their own volition and fill a definite and unchangeable place in the order and economy of nature. They play a brief rôle in the life of communities where they are placed; and however we may strive as physicians to arrest the hand of death, they pass from our sight and are no more. It is never a matter of lasting grief when men and women enfeebled by age or burdened with years die, after the companions of their youth and maturer years have departed, at the period when life brings little pleasure by reason of their weakness, sorrow, friendlessness or isolation. We can but feel that they are mercifully relieved of the burden of a life which they no longer enjoy and for which they are not fitted, and we do not repine.

When, however, eager young men, full of the joy of living, adequately prepared for their life work, filled with enthusiasm for study and anxious to relieve suffering and to better the conditions of mankind, are taken from us, we deeply and permanently mourn their loss and bow without resignation to a decree which we cannot explain. We can only hope that somewhere, somehow and at some time the broken threads of their promising young lives, so ruthlessly snapped, may again be joined together and woven into the enduring fabric of a higher form of existence which shall have no end.



I have been asked to say a word at the presentation of this tablet to commemorate the names of twenty-one young men who served the hospital as resident medical officers during the past quarter-century and who have passed from earth. I knew all of them and had watched their careers and the unfolding of their powers with the keenest satisfaction, and rejoiced in their rich promise of future usefulness. They were our close friends and companions and we all felt warm affection for them. We do not need this tablet to keep their memories green in our hearts, but we have gained permission to place a permanent

LIBRARY
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SIR WILLIAM OSLER.

From Sargent's portrait presented by Lady Osler on the Twenty-fifth Anniversary of the Hospital.

record here to be read by those who did not know them. This modest tablet is the tribute of their old friends and associates here. There used to be a similar tablet in one of the lecture halls of the old College of Physicians and Surgeons of New York, erected to the memory of those young medical men, nearly a score in number, who gave their lives for their profession while serving in the public hospitals of the city, which bore this heading: "Haec Mea Ornamenta Sunt." We, too, would claim these names as our jewels!

Death has indeed been busy during the past quarter-century in connection with the hospital and university. Not a single member of the boards of trustees of either foundation whom I met twenty-five years ago survives; President Gilman, Professors Newcomb, Rowland, Adams, Elliott, Martin, Brooks, Williams, have passed away, and many warm friends of the hospital and university in the city and state are no longer with us. And yet the duties and responsibilities which fell from their failing hands have been taken up by others, and the hospital and university are moving, active forces in the community as never before.

In the names of the associates and friends of the deceased members of the resident staff I desire to present this tablet to The Johns Hopkins Hospital.

RESPONSE BY DR. SMITH.

In accepting this memorial tablet on behalf of the trustees of The Johns Hopkins Hospital, I wish to express our gratitude to you and all others who have made this gift possible. It is a memorial which we shall always cherish.

REMARKS BY WILLIAM S. THAYER ON THE OCCASION OF THE PRESENTATION OF THE CRAYON PORTRAIT OF SIR WM. OSLER BY SARGENT.

The precious gift it is my privilege now to offer to the hospital is but another reminder of him who, though absent in person, has been with us and in us and around us in spirit from the beginning of this gathering.

What have been his contributions to medical science, what his inspiration and efforts and example have been to this institution, are so familiar to us all that it would be impudent to mention them. Would that we could put into words the influence that the man has had upon our lives! How much of that which is best in us is due to him and to his example! In all the fifteen years of my close and constant association with him I never knew him to do a hasty or an inconsiderate act, and I never heard him speak an unkind word of any man. Of how many can one say this? He is like Mactertine's true sage, in whose presence discord and strife and misunderstanding are impossible. In losing him we felt that we had lost our best friend and adviser, but he left us a legacy of tolerance and forbearance and charity that is among the richest of our possessions. This whole institution is replete with memories of the man; and no statue, no tablet, no portrait can bring him more vividly to our minds. But there will be others who follow after to whom our poor words will convey but a faint picture of that

which is a part of us. And so his old disciples welcome with heartfelt gratitude every new image which may help better to fix for posterity the presence of our dear chief.

The value of this new possession is greatly enhanced in that it comes to us through the thoughtful generosity of her who shares with him our lasting love and affection. Lady Osler of her own initiative has induced Mr. Sargent to make this replica of the portrait drawn by him for the College of Physicians in Philadelphia, and has sent it to us to-day. And so after all he is with us! We shall gain new inspiration from his counterfeit presence. Let us wait patiently in the hope that, four years hence, when the heavy clouds of the hour shall have rolled away, we may give him that welcome which our hearts hold for him to-day.

RESPONSE BY DR. SMITH.

It is needless for me to say that we can never have too many reminders of "our" Dr. Osler, whom we all love.

On behalf of all connected with The Johns Hopkins Hospital, I wish to express our gratitude to Lady Osler for presenting the hospital with this valuable and choice portrait. We shall cherish it as one of our choicest possessions.



REMARKS OF BLANCHARD RANDALL IN CONNECTION WITH A TABLET TO COMMEMORATE THE SERVICES OF D. C. GILMAN.

To tell of Mr. Gilman to this gathering is superfluous. As the first president of The Johns Hopkins University, his name is on every tongue. To his place as one of our foremost citizens for a full generation, generous, sagacious and helpful, the men, women and children of Baltimore can testify. Of his work here, his services, this tablet itself is a sufficient reminder, to commemorate which we are gathered here.

I well remember his words, so characteristic, to me in confidence in 1889. He said that to be allowed the opportunity "to direct the start of this institution, in loving mercy and tender pity to the sick and suffering," was one of the supreme pleasures of his life.

To paraphrase his own words, sent me after he was seventy years of age: This hospital "is now doubling the Cape of Good Hope which leads to a Pacific Sea, in whose bounds are the Fortunate Isles."

Mr. Superintendent: For the sake of the members of the house staff, present and to come, and the thousands who will receive help within our walls, the trustees of the Johns Hopkins Hospital, in grateful memory of Daniel Coit Gilman, place this tablet.

RESPONSE BY DR. SMITH.

Many of us had the good fortune to know Mr. Gilman. Most of those at present connected with the hospital did not, but all who are, or have been associated with this hospital know of his service in organizing and directing the beginnings of this institution. All who love the hospital, honor Mr. Gilman's memory and rejoice in having before us a permanent reminder of his service.

REMARKS OF L. F. BARKER AND W. S. THAYER ON THE DEDICATION OF THE MEDALLION TO THE MEMORY OF DR. JOHN HEWETSON.

DR. BARKER.

To my colleague Dr. Thayer and myself has been assigned the honor and the pleasant privilege of saying something about our friend and former co-worker, the late Dr. John Hewetson; it is to commemorate his life, his work and his personality that the beautiful medallion, made by Mr. Brenner, and subscribed to by a group of those who loved him, is to-day to be dedicated.

Of the group of medical men concerned in the actual work of The Johns Hopkins Hospital during its earlier years, all the senior members, with the exception of the great Billings, are, we are most thankful to say, living and actively engaged; but from among the junior members, as the tablet which Dr. Hurd has presented indicates, death has already made all too large a levy. We miss all the men who are gone, and we mourn their loss to medicine and to society.

To many of us, Dr. Hewetson's lingering and incapacitating illness seemed unusually distressing and tragical. As I remember him in the early "nineties," he seemed full of promise for a successful, a useful, and a happy career. Well started in Montreal, he came to Baltimore in 1890, and along with Lafleur, Thayer, Toulmin, Simon, Frank Smith and Hoch, found himself a member of that small group of men who, working under the inspiration of a great chief, William Osler, set the precedents which have made the medical department of this hospital a unique place in which to work. He was moderate, capable, industrious, modest, and loyal—qualities most desirable for the position which he had to fill.

At first he devoted himself conscientiously and entirely to the performance of the routine duties of the ward service, but as soon as the grooves of these had become well oiled, he turned to special studies—an analysis of the typhoid statistics of the hospital with Dr. Osler, and a study of the malarial fevers of Baltimore with Dr. Thayer. He followed with profit the courses in pathology and bacteriology given by Drs. Welch and Councilman, and in 1894, taking the advice of Dr. Osler and Dr. Mall, he went to Germany, where, in the Anatomical Institute in Leipzig, he took up the study of the finer structure of the nervous system, making excellent serial preparations

which, after his death, afforded the material for fruitful research by workers in Mall's laboratory.

But it was not Hewetson's medical work, good as it was, that singled him out as an unusual example among young men. That work was interrupted at too early a stage to permit us safely to prophesy how distinguishing it might have become. Rather than his work, it was the general conduct of his life, his forceful, and at the same time lovable personality, which distinctively marked him.

Behavior, as Bacon aptly described it, is the "garment of the mind"; it is the silent and subtle language by which the activity, the experience, and the purposes of the spirit are



revealed to those who can read it; it tells us what a man is, no matter what he purports to be.

When you met Hewetson, and tried to take his measure, you soon saw why everybody loved him; you began to do so yourself. His frank, open countenance, his cheerful good nature, his gentle courtesy, his self-security associated with obvious modesty, the evidences of integrity and of sincerity that radiated from him, and his assumption of well-meaning and of generous intention on your part, were excellences that could not fail to attract and to endear. There was magic in his eye; it beamed kindness; and there was no mud at the bottom of it. One felt that in Hewetson's presence and surroundings, high standards of conduct must be maintained. He was the kind of man whose approval you valued, and whose censure you would do your utmost to avoid.

In this beautiful work of art, now dedicated to Dr. Hewetson's memory, the sculptor has, I think, depicted some of the qualities to which I have referred. It must surely be of benefit to all of us at Johns Hopkins, where scholarship is so highly revered, to have, also, personality and behavior of the nobler sort extolled and commemorated. In days like these, when there are convulsive happenings in the world, when men are breaking faith with men, when the weak and the defenceless are being down-trodden, when not only the living men of many nations, but also the great works of man which have endured for centuries—pictures, books, cathedrals and universities—are being ruthlessly sacrificed, there is danger of our losing confidence in human nature; one begins to wonder if, in reality, our much-vaunted civilization is to founder on the rocks of hatred, arrogance, and mutual distrust. But we can be reasonably sure that it will not be so. Peace and freedom will eventually emerge. The spirit of which Dr. Hewetson was an exemplar will, we cannot but believe, ultimately triumph; and love, humility, and faith will regain their ascendancy in a purer, better world.

At this hospital we shall always cherish Dr. Hewetson's memory, and do all we can to foster the ideals of character and conduct for which he stood. That this bronze plaque, so full of artistic feeling and so sensitively executed, may contribute toward this end, those who present it, earnestly hope.

DR. THAYER.

There is little that one can say after the charming words of Dr. Barker.

I remember well Dr. Hewetson's entrance into the hospital family. Rather spare, not very tall but looking taller because of his unusually erect carriage and a fashion that he had from time to time of squaring his shoulders and throwing out his chest—he was a most engaging figure. His clean-cut features, the face, rather sharp with a peculiarly straight nose and a very sensitive upper lip—there was a charm about the man which I have rarely seen equalled. His eyes, which Dr. Barker has just mentioned and to which Dr. Osler referred yesterday, were wonderful clear eyes that looked directly at you and into which you looked away back into sparkling and mysterious depths. Fascinating eyes, with a gleam and a light in them that none of us who knew him can possibly forget!

He worked hard and faithfully in the hospital, and it was my happy lot to be thrown with him constantly. We undertook together an analysis of the cases of malaria which had occurred up to 1892, a study which we continued until 1894. I shall never forget the evenings which we spent about my desk going over the histories, writing out the summaries on long sheets of paper, and now and then dropping our work to step across the hall to chat with Barker.

It was in 1891 that Hewetson came to Baltimore. In the spring of 1894 he went to Europe to study at Leipsic, but in the summer he was called back again by some one of the many family misfortunes which one after another followed him. In the fall, however, he returned again, this time with Frank

Smith and me as companions. What a happy trip that was on the slow old steamer to London! Soon after we started, our party of three received a charming addition in Miss Julia Arthur, the distinguished actress. From morning till night we four sat upon deck listening to Smith's extraordinary stories and songs. I have often wondered if he could do it again. Hewetson was the life of the party as he was of every company.

That winter, alas, he was taken ill at Leipsic, and there Barker found him and carried him away to a restful spot in the mountains where he spent many months. In the following summer I visited him in his lovely resting-place above Montreux in Switzerland. He looked and seemed so well at that time that we were all hopeful that the malady had been arrested.

In 1896, after a trip as ship's surgeon to Australia, he joined his family in Riverside, California. But amid lovely surroundings cares and sorrows followed him, the illness and death of his father and sister and constant anxiety about his brother.

He was never able to return to work, and gradually and slowly, he grew weaker. But throughout it all he was never disheartened. There was never a note of discouragement in his correspondence. And how charming were his letters! No one could write as could Hewetson. I fancy that Barker and Smith have kept their letters. I know that I have mine, and I read them all but a day or two ago.

In 1905 a great joy came into his life in his marriage to Miss Susan Bacon. Nothing could have been more nearly perfect than his life during the few years which followed. The devotion of his wife brought to him the peace and the happiness which he so richly deserved, and his letters during this period were a delight. But, alas, this great happiness was but for a day, for in 1909 his wife, who had been delicate for several years, died. This crowning misfortune Hewetson received with the same calm and dignified resignation with which he had accepted all his other ills. But it was the end. He lingered but a year longer despite loving and devoted care, and died in the fall of 1910.

Through it all, as I have said, he was extraordinarily strong and courageous. The charm that we who knew him well had always felt, radiated out upon all with whom he came in contact. As we look back, those of us who were with him in the old days, we all feel that he was the finest and biggest and best figure of the early group of men who gathered here. He certainly was the best-beloved.

RESPONSE BY DR. SMITH.

In listening to the remarks of Drs. Barker and Thayer, I have had one thought, that Dr. Hewetson achieved the best that life offers—to be loved by all who knew him. Few of those now on the hospital staff had the pleasure and privilege of being associated with him or of knowing him, but this beautiful memorial of the man cannot fail to have its effect

upon all who are to live and work together under its benign influence. I am sure that all will profit by remembering the example and high standards which he set for us during his life here.

On behalf of the trustees of The Johns Hopkins Hospital, I beg to express our grateful appreciation to those who have

presented the hospital with this beautiful medallion in memory of Dr. Hewetson.

NOTE.—The papers in detail which were presented at the sectional meetings in the various departments of the Hospital, including the Training School for Nurses, will be published early in the coming year in a special number of the BULLETIN.

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